Metabolic Disturbances in Clinical Medicine

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With 35 illustrations



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PREFACE

THERE are several excellent textbooks concerned with metabolism but they tend either to deal with metabolic diseases (using the term disease in the sense developed in the medicine of the nineteenth century) or to deal with metabolic abnormalities and disturbances from the point of view of the biochemist The present book attempts to steer a course between these two and to describe for the practising clinician some of the more important of those disturbances of metabolism which he may encounter in the course of his work It is of course impossible and undesirable to be confined by any hard and fast barriers and therefore it has at times been necessary to enter into certain biochemical details and at others to describe so called metabolic diseases Nevertheless it is hoped that the physician who has not specialized in this aspect of medicine will be able to gain some insight into its more recent developments and to obtain definite practical help in diagnosis and in therapy

The metabolism of disease is one of the most rapid growing points of internal medicine and a complete presentation is beyond the scope of any textbook A book suitable for the purposes outlined above should be neither too large nor too expensive and thus inevitably there must be many omissions In selecting suitable subjects duplication has so far as possible been kept to a minimum Thus there is no section devoted specifically to the alimentary tract for many of the results of for example malabsorption are dealt with in other connections Nutrition being the study of those substances forming the necessary raw materials for metabolism and endocrinology the study of the system devoted to the chemical regulation of metabolic processes are vast subjects in themselves and no attempt has been made to consider them in isolation instead they are woven where appropriate into the general theme Selection of material has also been made as a result of experience in both undergraduate and postgraduate teaching so far as possible those subjects of common importance which are least understood being included

It is difficult with a very rapidly advancing subject to include all of the most recent knowledge in a book of this kind There are inevitable delays which are more annoying and frustrating to the contributors than to anyone else since they mean constant revision if the writing is still to be topical at the time of publication Every effort has been made to ensure that this is so and the opportunity is taken here of thanking

the contributors for all the efforts which they have made to this end I would also like to thank those authors editors and publishers who have kindly allowed illustrations from their works to be reproduced

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CONTENTS

CHAPTER		PAGE
1	Problems of General Nutrition in Clinical Medicine	1
2	Disturbances of Water and Electrolytes, Aldosterone and Aldosteronism	15
3	Metabolic Aspects of Renal Disease	44
4	The Metabolic Disturbances following Injury	72
5	Metabolic Aspects of Liver Disease	111
6	Cardiovascular Aspects of Metabolic Disease	146
7	Oedema in Chronic Congestive Heart Failure	156
8	Atherosclerosis	166
9	Lung Function and Acid base Balance	172
10	Oxygen Therapy	179
11	Metabolic Bone Disease	198
12	Metabolic Disturbances and the Haematopoietic System	213
13	Disturbances of Metabolism affecting the Central Nervous System	287
	Index	347

CHAPTER 1

PROBLEMS OF GENERAL NUTRITION IN CLINICAL MEDICINE

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The Calorie Balance

Since energy is derived from chemical processes it is inevitable that the body should maintain a calorie balance with its environment This fundamental concept can be represented as follows

Calorie value of food intake = heat output (cal)
+ *calorie value* of urinary organic chemicals
+ calorie value of faecal organic constituents
+ change in calorie value of body tissue

In normal health the body weight remains substantially constant over long periods of time and under these conditions the proportions of various tissues do not significantly change It follows therefore either that the calorie value of food intake is accurately correlated with energy expenditure or that if the calorie intake varies there must be a corresponding variation in one or more of the three other terms of the equation It can easily be shown experimentally that substantial changes in calorie intake are not associated with any corresponding change in the calorie value of faeces and urine It is technically a good deal more difficult however to measure the total heat output of the body over long periods of time and the question has often been posed whether changes in calorie input are followed by compensatory changes in heat output The chemical processes involved in the metabolism of nutrients require in themselves a certain amount of energy particularly in the case of protein materials (the specific dynamic action) so that to some extent there may be an increase in heat production and loss with an increase in calorie intake This however is small and is in no way sufficient to maintain the equilibrium of the equation The possibility of any additional change in heat loss in association with an alteration in calorie intake has been carefully investigated by many workers in particular by Wiley and Newburg (1931) and more recently by Pass

more, Meiklejohn, Dewar and Thon (1955) There has in fact been no evidence of substantial change either in basal metabolic rate or in the metabolism resulting from activity, which would compensate for changes in calorie intake

The evidence fully summarized by Newburg (1942) would thus seem to point to the likelihood that calorie balance is ultimately maintained to the largest extent by regulation of the intake This would appear superficially to be a somewhat surprising conclusion at variance with everyday experience During discussions of this kind one is always reminded of people who remain lean despite a large appetite, and of others who tend to become fat although their food intake is only moderate The work already quoted however by Passmore and his co workers was carried out on lean individuals who were able to increase their calorie intake from 2100 to 4000 per day There was no evidence of a significant increase in metabolism nor decrease in absorption resulting from the increased intake of calories and the subjects did in fact gain weight, although not as much as would have been expected from a consideration of their calorie balance Moreover it has been shown by McCance and his associates (Edholm Fletcher Widdowson and McCance, 1955 and Boovens and McCance 1957) not only that the basal metabolic rate of normal individuals may depart from the average of normals much more than was at one time anticipated but that the amount of energy expended when lying sitting standing or at other forms of exercise might also be very different from individual to individual Thus different people outwardly similar, might expend very different quantities of energy although their activities might not appear to be so very different Those who carry out their daily activities efficiently in the physical sense require a smaller calorie intake to maintain weight than their more thermodynamically inefficient counterparts This does not mean that persons who tend easily to get fat necessarily use less energy in standing sitting or lying etc than thin people such people evidently have an appetite which tends to cause them to ingest more calories than in fact they require

It is important, therefore to inquire into the mechanism of appetite regulation and of satiety and into any other factors which control the amount of food which is eaten It is obvious that the capacity of the organism itself will set crude outer limits to the intake of food and it may be that this partly determines the frequency with which patients who have had a partial gastrectomy are found to be underweight However that the crude mechanical limitation of stomach distension is not crucial in the normal animal has been suggested by Adolph (1947) He showed that in young rats the calorie content of the diet seemed to be the overriding factor which governed the amount of food ingested

Nor would it appear that hunger contractions which have been

shown to exist both in animals and in man (Quigley 1955) and which greatly increase the drive to obtain and eat food are more than a crude but urgent mechanism which tends to set a lower limit to the food in take They would certainly seem to be of minor importance in com munities where food is easy to come by

In 1940 Hetherington and Ranson discovered that animals with cer tain lesions confined to the hypothalamus would become obese and this obesity was shown by Brobeck Tepperman and Long (1943) to result from hyperphagia Subsequent work suggested that another centre existed in the hypothalamus destruction of which caused aphagia (Anand and Brobeck 1951) On the basis of these findings it has been suggested by Brobeck (1955) that two centres exist one a satiety centre situated medially destruction of which causes hyper phagia by increasing the level of satiety and the other an appetite centre situated laterally destruction of which will cause aphagia be cause of a complete lack of appetite Thus increased food intake may result from overactivity of the appetite centre (more frequent eating) or from underactivity of the satiety centre (bigger meals) by contrast the intake of food will be decreased if the appetite centre is underactive or if the satiety centre is overactive so that smaller meals are eaten How the particular activity of each of these centres is controlled so that the normal precise calorie balance is maintained has not yet been shown Brobeck (1948) has suggested that it is the specific dynamic action of the ingested food which is mainly responsible that a centre is sensitive to temperature changes Although it is possible that this may be one factor Kennedy (1952) has produced evidence which would suggest that it probably plays only a minor part if any and seems to be of little im portance when causes of experimental obesity are considered The work of Gasnier and Andre Mayer (1939) would suggest that there is a short term day to day regulation of food intake dependent in some way upon energy requirements and that there is in addition a long term mechanism which can correct errors in the day to day regulation and which is related in some way to body weight

Jean Mayer (1955) has put forward evidence suggesting that appetite is dependent upon the rate of utilization of glucose Thus there will be no desire to eat when glucose is being rapidly utilized—when there is a large difference between concentrations of glucose in arterial and venous blood by contrast an increase in appetite will occur when there is little difference between these concentrations (Van Itallie Beaudoin and Mayer 1953 and Mayer 1953) It should be noted however that several investigators have failed to suppress food intake in animals or subjective desire for food in humans (Bornstein and Grossman 1956) by means of intravenous infusions of glucose It was also noted by Bruce and Kennedy (1951) that apart from changes in palatability or

gross adulteration the calorie intake of hyperphagic or lactating rats remained much the same regardless of the composition of the diet This would suggest that metabolites other than glucose might be involved in the regulation of food intake

Kennedy showed that his hypothalamic rats ate ravenously whilst they were gaining weight i e during the dynamic phase of their obesity Eventually however having reached a state of considerable obesity the static phase the food intake dropped so that it was not very different from that of a normal rat When such rats were underfed they lost weight only to regain their excessive appetite so that when again fed *ad libitum* they would eat large quantities until they had again regained their former excessive weight Adulteration of the food by means of kaolin during the dynamic phase resulted in greatly increased intake so that the total calorie intake remained much the same, when the static stage had been reached however adulteration resulted in a decreased calorie intake and weight loss These findings would indicate that even these animals with a damaged hypothalamus have some form of regulation of body weight that they have a preferred weight at which they tend to remain as a result of changes in food intake

It has also been found (Kennedy 1952) that intact rats nursing litters of ten to twelve in order to produce maximum lactation ate even larger quantities than rats rendered hyperphagic from hypothalamic damage Furthermore if the medial hypothalamic nuclei of such rats were damaged there was no marked tendency for them to become obese until lactation had ceased Rat milk has a high fat content and it seems possible that the maximum rate of disposal of fat might be a factor which limits food intake

Adipose tissue thought at one time merely to be a relatively inert storehouse of excessive calories has been shown in fact to be an active tissue in dynamic equilibrium with the rest of the body Wertheimer and Shapiro (1948) and Bates Mayer and Nauss (1955) have produced evidence which suggests that under conditions where food is freely offered the amount of fat mobilized daily is proportional to the total size of the fat depots and the findings of the latter group of workers also suggest that there are probably metabolic differences in different types of experimental obesity It is suggested that the accumulation of excessive fat in hypothalamic rats and gold thioglucose mice is largely secondary to the hyperphagia whereas in mice of the hereditary obese type there is an inherent metabolic defect with increased synthesis and decreased mobilization of fat As pointed out by Mayer these findings are complementary to those of Alsonso and Maran (1954) who found that hereditary obese hyperglycaemic mice after prolonged periods on restricted diets so that they weighed 30% less than their control litter mates nevertheless had several times more fat than these controls

Clinical Considerations

The experimental and chemical considerations discussed above are likely to have in due course some importance in the clinical field In man however other factors such as food habits and emotional changes assume a greater importance than would appear to be the case in animals It is not proposed to discuss weight change arising from hypothalamic lesions or endocrine abnormalities attention will be con fined to a consideration of so called simple obesity and to the effects of marked loss of weight

It is important however that consideration should first be given to the criteria by which a subject may be said to be underweight or over weight Figures for the mortality rates and the incidence of various dis orders in relation to body weight are largely derived from insurance statistics and are thus mainly concerned with deviations in body weight for height from the average There is no justification for accepting the average as the ideal indeed there is much to suggest that the average weight is higher than the ideal weight (the ideal weight being that associated with the minimum amount of physical disability and the greater longevity) in most countries where the food supply is relatively plentiful (Marks 1956) Ideally one would like to obtain some know ledge of the amount of adipose tissue present of the amount of extra cellular fluid and of the amount of bone The rest of the body weight would be made up of more or less metabolically active tissue These estimations might be of particular importance if the results produced by Kurlander Abraham and Rion (1956) which suggest that in *men* com ponents in body build other than adipose tissue are the factors which produce the association between a heavy body weight and a high in cidence of cardiovascular disease are shown to be correct

Estimates of the total amount of adipose tissue in the body have been made by measurements of body specific gravity—either by weighing the patient under water or by estimating his total body volume This latter estimation is carried out by placing the patient in an enclosed space of known volume and measuring the pressure of air in the enclosure a tap is then opened which joins this space with another of known volume containing air at a known and different pressure from the vessel enclos ing the patient The final equilibrium pressure in the whole system is read and from the figures obtained the volume of the patient can be determined The temperature of the system must of course be carefully controlled Estimates of the proportion of total body weight contri buted by adipose tissue then depend upon the assumption that the specific gravity of the lean body mass is 1 103 whereas that of adipose tissue is 0 93 (Behnke Osserman and Welham 1953) It is obvious that these are only approximate assumptions and are likely to be more or less correct only if there is no abnormality of water and electrolyte

metabolism involving an increase in extracellular fluid on the one hand or dehydration on the other

Since it has also been found that the proportion of water in the lean body mass is 72%, and since, apart from a small amount of extra cellular fluid adipose tissue is almost anhydrous the proportion of adipose tissue in the body has been estimated from measurements of total body weight and total body water—the latter being measured by the dilution of substances such as heavy water, urea or antipyrine, which are evenly distributed throughout all the water phases of the body Again this method of estimation suffers from grave errors in the presence of abnormalities in water metabolism and consequently it has been refined by estimating total body water *and* extracellular water (inulin or thiocyanate space) and thus intracellular water—which is much more constant constituting about 67% of the lean body mass and being virtually absent in adipose tissue (McCance and Widdowson 1951)

Probably the most useful means of estimating adipose tissue for clinical use is by measuring skin fold thicknesses This method has been investigated in particular detail by Edwards (1950) who has designed a special caliper which exerts a constant pressure (10 g per mm²) be tween its jaws (Edwards Hammond Healy Tanner and Whitehouse 1955) by Brožek (1955) by Brozek and Keys (1951) by Garn (1954) and by others The skin fold is some measure of the thickness of two layers of skin plus two layers of the underlying subcutaneous tissue and of course it varies greatly from one part of the body to another From these measurements some estimate can be made of body density and thus of total body fat (Pascale Grossman Sloane and Frankel 1956) certainly for young men A serious disadvantage however, consists in the fact that no allowance can be made for relatively greater deposits of internal fat which occur with increasing age nor is the method suitable in cases of endocrine abnormality in which fat distribution might be quite abnormal

Edwards (1956) considers that when a change in body fat occurs as a result of a change in calorie balance all the cells of adipose tissue are equally affected and that there is thus a proportionate change in skin fold thicknesses at all sites This view is supported by the work of Garn (1954) who found that the pattern of fat deposition changed little during a weight drop of as much as 11%

Suggestions have also been put forward whereby a clinical estimate of skeletal size and of musculature can be made Body height and the greatest distance between the lateral margins of the iliac crests are prob ably the best indicators of the size of the skeleton, and the diameter of the upper arm corrected for skin fold thickness can give a good estimate of musculature (Recommendations 1956)

Simple Obesity

Whether from emotion from habit or from some underlying as yet undetected metabolic abnormality resulting in a wrong control of body weight simple obesity is one of the commonest nutritional problems in those countries where food is easy to obtain The ill effects on general health on morbidity and mortality are well known and will not be con sidered in detail Very little work has been done on the long term effects of weight reduction in obese people for only a small proportion of obese people do in fact reduce their body weight to normal and keep it there It has been shown by Fellows (1931) however that those who maintain a reduced weight suffer less from those conditions known to be associated with obesity than similar subjects who remained obese It would also appear that a small but significant fall in blood pressure may occur with weight reduction (Adlersberg Coler and Laval 1946 Ley 1939) There has been some criticism of this view partly because change in the arm diameter will affect the blood pressure reading as obtained by the usual indirect method but Danowski and Winkler (1944) do not consider this factor to be of much significance It is of course also well known that the diabetes of obese diabetics may show a very considerable improvement with weight reduction Dublin (1953) in a careful statistical appraisal of the mortality rates of obese subjects who reduced their weight concludes that the resultant mortality rate was considerably less than that of those subjects who did not reduce

A perusal of the literature reveals how difficult it is to induce obese patients to lose weight and to maintain the lower weight which they may attain In general it is probable that the long term failure rate is in the order of 70–80% (Rony 1940) Although various substances are now available which appear to depress appetite it has been the experi ence of the author that one is doomed to failure unless the patients can be completely and utterly convinced that they must lose weight and are consequently prepared to make the necessary effort of will to restrict food intake As a rule the first three to five weeks are the most difficult and patients should be informed of this During this time they feel hungry sometimes light headed and weak and they become very sensi tive to cold Sub equently after weight reduction has taken place these patients must control their food intake by measurements of body weight If appetite is relied upon they will revert to their previously obese state

From the considerations given above it would appear that a diet in volving a simple and adequate reduction in calorie intake would be sufficient to cause a reduction in body weight Provided such a diet contains enough protein the weight loss accrues solely from a loss of fat cellular tissue is not broken down (Newburg 1944) Exact and

elaborate diets have been constructed which will do this and naturally, where the psychology of the situation is so important some will be more suitable than others for any individual patient However in general the author has found that patients tend not to confine themselves to diets which are too rigid too elaborate or too far removed from an ordinary dietary regime The most flexible and easily understood diet and one which invites a considerable degree of collaboration from the patient is that devised by Marriott (1949) This is in fact more a guide to eating than a therapeutic diet and in practice it has been found to work very well producing a fall of some 2–4 lb in body weight per week

MARRIOTT S REDUCING DIET

1 Eat or drink as much as you like (or can get) of

Lean meat poultry game rabbit hare liver kidney heart sweet bread—cooked in any way but *without the addition of flour bread crumbs or thick sauces*

Fish (not tinned) boiled or steamed only *no thick sauce*

Eggs boiled or poached *only*

Potatoes boiled steamed or baked in skins but *not fried roast sauté or chips not potato powder*

Other vegetables of all kinds (fresh tinned or dried) cooked in any way not involving the use of fat

Salad and tomatoes *without oil or mayonnaise*

Beetroot radishes watercress parsley

Fresh fruit of any kind including bananas Also bottled fruit if bottled without sugar *Not tinned or dried fruits (including dates figs and raisins)*

Sour pickles *not sweet pickles or chutneys*

Clear soup broth Bovril Oxo Marmite

Salt pepper mustard vinegar Worcester sauce (*no other sauces*)

Saccharin for sweetening

Water soda water and *non sweetened* mineral waters

Tea and coffee (milk only as allowed below)

2 You may have milk (not condensed) up to half a pint daily
No cream

3 You may have three very small pieces of bread per day and take them either one at each main meal or all three at one meal as desired (very small means *not exceeding* 1 *oz*)

4 You may have *nothing else whatever* particularly note that this means

No butter margarine fat or oil (except for cooking meat *not fish*)

No sugar jam marmalade honey sweets chocolate cocoa

No puddings ices dried or tinned fruits nuts

No bread (except as above) cake biscuits patent reducing breads cereals oatmeal Albran Ryvita Vitawheat

No barley rice macaroni spaghetti semolina sausages cheese
No cocktail savouries alcohol (beer cider wines and spirits)

Weigh before you begin and thereafter weekly on the *same scales* in the *same clothes* and at the *same time of day*

Some authors have suggested that better results can be obtained by restricting carbohydrate and giving a lot of fat In particular Pennington (1953) summarized evidence which suggests that there may be some metabolic abnormality in obesity He further postulates that in obese subjects there is a lowered rate of mobilization of fat per unit of adipose tissue and that this is compensated for by an increased total of fatty tissue Obesity he suggests might be considered as a compensatory hypertrophy of adipose tissue allowing for an increased use of fat by a subject who suffers from an impairment in the ability to oxidize carbohydrate Acting upon this theory he prescribes a diet in which only carbohydrate is restricted Protein and fat are allowed *ad libitum* He finds that patients on such a regime derive roughly 80 / of their energy from fat and 20% from protein The total calorie intake varies from 2000 to 3100 calories per day Each of the three meals of the day contains 6–9 oz of lean meat and 2–3 oz of fat (cooked weight) In addition not more than 60 g of carbohydrate may be taken in the day On such a regime he claims that patients lose weight satisfactorily at a rate of about 2 lb per week moreover they do not show the usual tendency to relapse which is so common on diets based on a simple reduction in calories Recently Kekwick and Pawan (1956) have published some curious findings with regard to the rate of weight reduction of obese individuals on isocaloric diets of varying fat protein and carbohydrate content They kept the water and salt intake constant and measured total body water by the urea dilution method of McCance and Widdowson (1951) They found that patients lost weight more rapidly when they were on a high fat diet than when they were on a high protein or high carbohydrate diet of the same total calorie value Moreover whereas five obese patients maintained or slightly gained weight over a seven day period on a 2000-calorie diet containing similar proportions of protein fat and carbohydrate to that found in an average diet four of them actually lost weight when the calorie value was increased to 2600 per day there being increased proportions of fat and protein in the diet Measurements of body water by the urea method revealed that its proportion to body weight remained unchanged There was no difference in the proportion of nutrients absorbed and measurements of BMR revealed no significant difference when the patient was on the different diets The insensible loss of water was estimated in some patients and it was found to increase when the diet was high in carbohydrate and fat Calculation shows that the difference in the latent heat

of evaporation is insufficient to account for the discrepancy in apparent calorie balance but the authors feel that the difference in insensible water loss is some evidence of a change in metabolism

In summary it may be said that although in the last resort gain or loss of weight is a question of calorie balance, to regard this as the whole problem is grossly to oversimplify the situation As a practical measure however restriction of calorie intake will produce a fall in body weight and although a high fat intake may in some way also result in loss of weight in obese persons, a good deal more investigation is needed before this method of slimming should be generally applied, in particular the effect of such diets on the production of arterial disease needs careful elucidation

Loss of Weight

Just as simple obesity results from an intake of calories greater than metabolic requirements so loss of weight may result from the opposite from the ingestion of fewer calories than are required Loss of weight can also occur however if the metabolism becomes deranged or if there is a deficient intake of some essential nutrient so that either the full utilization of the calorie value of ingested nutrients becomes impossible or certain tissues are unable to maintain themselves in the normal fashion The appetite is of course nearly always depressed in these situations

The effects of undernutrition have been very fully described by Burger Drummond and Sandstead (1948) Keys Brožek Herschel Mickelsen and Taylor (1950) and by McCance (1953) among others The observations were made on subjects who were living under famine conditions or who were experimentally subjected to an over all deficiency in food intake The syndrome described therefore was that which arose in previously healthy subjects and thus hunger and mental changes associated with an intense drive for food were very prominent These naturally are not frequently found in clinical conditions associated with inanition since other factors such as toxaemia, an initial anorexia or nausea and vomiting are usually present Nevertheless the physical changes resulting from the inanition are usually seen in malnourished patients whatever the cause

If the patient is obese the first stage of inanition consists in a loss of body fat, for even when the protein intake is quite low there may be no net loss of nitrogen during loss of weight in obese subjects Thereafter the patient begins to lose nitrogen in excess of intake and since this is accompanied by a loss of potassium in protoplasmic proportions it would seem that a break down of cellular material was occurring Animal studies would indicate that the greatest loss occurs from voluntary muscles the heart and the alimentary tract On the other hand

histological and biochemical evidence suggests that there is no significant decrease in the actual number of cells A striking feature is a marked increase in the extracellular fluid content of the body which is not necessarily associated with oedema of the dependent parts but which can effectively mask at least for short periods the changes in body weight which would accrue from changes in cell mass In due course there may be a fall in the level of serum proteins but this is not usually marked nor is the electrophoretic pattern very different from that found in normal subjects There is a good deal of controversy as to the cause of the increased extracellular fluid volume and of famine oedema There is little correlation between the serum albumen and protein levels and the presence of oedema nor is the oedema fluid rich in protein which one would expect if there were an increase in capillary permeability Venous pressure is lower than normal in semi starvation but there have been no direct measurements of intracapillary pressure The total volume of extracellular fluid seems to remain much the same as it would have been if the individual had been normally nourished and it has been suggested by Ancel Keys and his co workers that this volume remains more or less constant whereas the volume of the other body tissues decreases They do not make any suggestions about the mechanism whereby this is brought about

The basal metabolic rate tends to fall and may decrease to some 40 % of its pre starvation level When this is expressed on the basis of unit surface area or of unit weight a good deal of the apparent fall results from the much higher proportion of extracellular fluid in the body However when correction is made for this and the metabolic rate per unit of active tissue is ascertained there still seems to be a small though definite fall

When the intake of protein is reduced it has been found that a fall in nitrogen output does not occur for some two to three weeks When equilibrium has been reached a normally nourished but not obese individual at rest in bed goes into negative nitrogen balance when the calorie intake is less than about 2400 in semi starvation this falls to something like 1600 calories it must be emphasized however that there are very great individual differences and as has been discussed above very low calorie intakes do not result in nitrogen loss in obese people

Clinically apart from the intense drive to obtain food which occurs in conditions of famine and emaciation the most striking feature is general muscular weakness and decrease in physical activity There are no significant changes in intellectual functions but there is a considerable disinclination to use these faculties The skin if it has been exposed to the weather becomes crackled dry and scaly a mild degree of follicular hyperkeratosis may occur and sometimes brown pigmentation

develops round the mouth on the malar regions and under the eyes Lanugo tends to grow on the body and the axillary and pubic hair becomes somewhat more sparse although it is not decreased to the degree found in hypopituitarism the hair on the head may be dry and staring and peripheral cyanosis is often present The blood pressure falls and if previously normal will become hypotensive there is a bradycardia Temperature regulation becomes faulty so that in cold conditions body temperature is somewhat lower than normal whereas in hot climates it may be higher Undernourished subjects always seem to be very sensitive to the cold A mild degree of anaemia may be found Occasionally enlargement of the parotid glands occurs and in men gynaecomastia Nocturnal polyuria tends to be a prominent feature under famine conditions and in populations precedes the onset of famine oedema This may in part be due to the large amounts of soups and similar concoctions which are ingested in these circumstances Sexual libido becomes diminished and then absent and in females amenorrhoea is common In extreme degrees of starvation a watery diarrhoea with faecal incontinence ensues

The degree of emaciation which can take place and which can nevertheless be followed by recovery is not certain In general it would seem that about 50% below the standard weight for height in the lower limit (McCullagh and Tupper 1940) but occasionally even more severe degrees of weight loss have been followed by recovery

Rehabilitation of the Undernourished

It had been thought that persons who had been the victims of semi starvation would be unable to digest adequate quantities of normal foods when they were presented In fact this idea was shown to be erroneous and no advantages were found for predigested preparations If too great an intake was allowed however diarrhoea might occur and sometimes during the period of rehabilitation oedema and heart failure appeared

From experience in Europe and from the results of the Minnesota Experiment carried out by Ancel Keys and his co workers it would appear that the most important factor in general inanition is to increase the calorie intake This however should not be too great since cardiac decompensation may be induced and since there seems to be little gain in recovery rate with increasing calorie intake certainly over about 3000 Indeed with too great an intake of calories there seems to be a disproportionate gain in body fat content and little or no acceleration in the return to normal of lean body mass of muscle strength or of over all endurance It would also seem that provided the rehabilitation diet is satisfactory in its protein content (75 g per day or thereabouts) and provided that it has the vitamin content of a satisfactory normal

diet there are no advantages to be gained from giving protein or vitamin supplements

Naturally under clinical conditions specific nutritional defects may occur along with general inanition under these circumstances extra supplies of the deficient nutrient should be given But in general it would seem that the attractive presentation of well cooked appetizing high quality foodstuffs is much the most important step in the nutritional rehabilitation of an undernourished patient

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CHAPTER 2

DISTURBANCES OF WATER AND ELECTROLYTES

D A K BLACK

A CONVENTIONAL approach to medicine and surgery is based very largely on the subdivision of the patient into a number of systems each with its corresponding diseases but the convenience of this systematic approach is bought at the cost of considerable distortion of the actual patterns of disease as we see them in the sick man Medical progress is straining against these artificial barriers in many directions we may instance the modern outlook on rheumatism on hypertension or on diabetes in which the joints the arterioles and the pancreas are no longer thought of as diseased organs adequate to explain the syn dromes but as victims of generalized abnormal processes which distort the activity of several tissues organs and systems In this chapter we have to consider a number of disturbances of body fluid which exemplify just this type of process which transcends the divisions of bodily form and function with which we become familiar as students Disorders of body fluid impinge in some degree on all the various specialities which make up practical medicine but the business of everybody is the busi ness of nobody and the prevention and correction of disorders of body fluid may at times fall short of perfection The mistakes which I have seen—and made—in the control of fluid balance have arisen more often from inadequate knowledge than from lack of biochemical data and I propose to lay emphasis on physiological principles and clinical syndromes rather than on the detailed biochemistry of body fluid dis orders It is in any case much safer to treat patients on the basis of what they feel and show than to treat laboratory reports or fluid balance charts

The expression body fluid denotes not only the more obviously fluid components of the body such as plasma intestinal juices and CSF but also the electrolyte in water medium which enters into all the solid tissues and in fact accounts for most of their mass Not only does body fluid maintain turgor by its presence and transport of food and metabolites by its circulation it also takes a direct part in metabolic activity and the electrolyte composition of body fluid can influence the rate of enzyme action The composition of body fluid is in turn quite considerably influenced by the metabolic activity of tissues The very

striking preponderance of sodium in extracellular fluid, and of potassium in intracellular fluid, is no longer attributed to impermeability of the cell wall to these cations but is recognized as the consequence of a continuous active extrusion of sodium or indrawing of potassium by cellular metabolism when this is arrested the characteristic difference in electrolyte composition between extracellular fluid (ECF) and intracellular fluid (ICF) is no longer maintained A decrease in the serum sodium level is not uncommon in gravely ill patients who have not lost salt from the body and they may also have some increase in the serum potassium these changes may well be due to depression of cellular activity We shall mainly be concerned however with body fluid disorders in which external losses or gains of water and electrolyte are the primary cause of trouble and changes in body fluid distribution within the body are consequential

Amount and Distribution of Body Fluid

Methods of measuring total body water, based on the apparent volume of distribution of heavy water, have given average values of 61% in young men and 51% in young women (Edelman *et al* 1952) The proportion of water in the body declines with age being highest in infants obesity diminishes the proportion of water in the body and this may account for the sex difference just quoted These results agree well with earlier work mainly on animals in which the loss of weight on desiccation of a carcass has been determined The over all percentage of body fluid is not perhaps very significant in comparison with its distribution Differentiation of body fluid into extracellular and intracellular fluid is fundamental to any understanding of clinical body fluid disorders In Fig 1 I have attempted to set out the relative amounts of fluid in these two compartments and in the same diagram I have included the usual concentrations of sodium and potassium in the two types of fluid We must now try to explain why electrolyte concentrations must be introduced into even the simplest description of body fluid and also why these concentrations must be expressed in mM /L or m equiv /L before they can be used in this way

Osmotic Pressure

It is agreed that the walls of most body cells permit the free passage of water so the balance between extra and intracellular water must depend on the relative vapour pressure outside and inside the cells The vapour pressure of an aqueous medium is lowered by dissolved substances so that water will flow from a medium of low concentration to one of higher concentration This osmotic attraction or osmolarity of a solution is dependent on the number of particles of a dissolved substance in a standard volume of solution The number of particles

depends not only on the concentration of a given dissolved substance in g /litre but also on its molecular weight since the *number* of particles is important and not their size if a substance of high molecular weight such as a protein and a substance of low molecular weight such as urea are each present in the same concentration by weight/volume there will be very many more particles of urea (MW 60) than of say

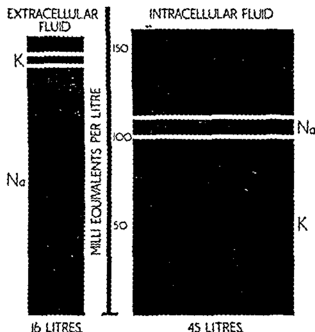


FIG 1 Relative amounts of sodium and potassium in extra cellular and intracellular fluid The width of columns represents volume, and their height concentration of electrolyte in m-equiv /L the total amounts of Na and K in the two compartments are thus represented by area The unmarked portions of the columns re present other cations mainly calcium and magnesium

haemoglobin (MW c 80 000) The electrolytes of body fluid are low molecular weight substances moreover they are almost completely dissociated into ions so that a notional molecule of salt in body fluid would actually constitute two particles a sodium and a chloride ion This combination of low molecular weight and high dissociation in the salts of sodium and potassium found in body fluid gives them a position of predominance in determining the osmolarity of body fluids and so indirectly the amount of fluid in the two great compartments If we take plasma the molar concentration of protein is 2 mM /L of urea 5 mM /L but sodium accounts for 140 mM /L by itself and its

associated anions for a further 140 mM /L These somewhat arid figures contain within them the secret of that Companionship of water and electrolytes (Gamble 1951) which is so essential a feature of the organization of body fluid

When we recall further that the amount of protein by weight in plasma is about seven times that of sodium and chloride we can see the difficulties we impose on ourselves if we keep on expressing electro lyte concentrations in terms of weight and not in terms of the number of particles concerned which is what really matters not only in osmotic equilibrium but also in ordinary chemical combination Plasma electrolytes are not estimated gravimetrically, so that it is no more difficult to express the results in molar notation than in terms of weight We shall use molar notation consistently in this presentation but some laboratories still report electrolyte results in mg /100 ml or in even more bizarre notations such as mg NaCl/100 ml or vol CO_2/100 ml In order to convert mg /100 ml into millimoles per litre (mM /L) we have only to multiply by 10 and divide by the atomic weight of the ele ment concerned Osmotic relationships are appropriately considered in mM /L but when we are dealing with chemical combination as in acid base balance we must also take into account the valency or chemical combining power of the ion With univalent ions such as sodium potassium chloride and bicarbonate, there is no difficulty as the numerical value for millimoles/litre (mM /L) is the same as for milli equivalents/litre (m equiv /L) With divalent ions such as sul phate the equivalent weight is half the atomic weight so that the value in m equiv /L is twice the value in mM /L in other words a divalent *ion counts as two in chemical combination but only as one in* deter mining osmolarity At the pH of plasma both phosphate and protein are anions with valencies of about 1 8 and 8 respectively at other pH values as in the urine the valency of these anions changes but in this review we shall not be concerned in any detail with the acid base balance in urine It is perhaps fortunate for the chemically naive (in cluding the author) that the main structural electrolytes of body fluid are univalent and so have the same osmotic and chemical potency

Electrolyte Composition of Body Fluid

Now that we have equipped ourselves with a terminology appropriate to the function of electrolytes in body fluid we can examine further the differences in composition between the different phases of body fluid Although there are minor differences in electrolyte composition of plasma and extracellular fluid occasioned by their very different protein concentration for the present purpose plasma can be taken as repre sentative of ECF Sodium is the predominant cation, and potassium

calcium and magnesium make up the total cation to about 150 m equiv /L About two thirds of this is balanced by chloride and the remainder mainly by bicarbonate though phosphate sulphate organic acids and protein also balance significant amounts of cation From analysis of 50–100 samples of normal blood Wootton and King (1953) give the following concentrations of the main electrolytes in plasma

	Range (includes 98% of results)
Sodium	133 –152 m equiv /L
Potassium	3 5– 5 6
Chloride	99 –108
Bicarbonate	24 – 31

Our knowledge of the electrolyte composition of intracellular fluid is less precise because a pure sample of this fluid cannot be obtained Most of the estimates are based on tissue analyses in animals and these involve a correction for the extracellular fluid which is inevitably present in the tissues A few analyses of human muscle biopsy material which involve a similar correction are also available and numerous analyses of washed human erythrocytes have also been made Although there is general agreement between the various methods it is probably fair to say that we have a good qualitative knowledge rather than a strictly quantitative account of the electrolyte composition of intra cellular fluid Because of the large bulk of muscle in the body muscle ICF forms more than half the total and the composition of muscle ICF is probably representative of tissues which are comparatively in active metabolically Tissues such as liver and kidney with high meta bolic activity have probably got a less constant ICF composition and in them the osmotic concentration within the cells may be higher than that in the surrounding ECF the osmotic gradient requiring meta bolic energy for its maintenance (Robinson 1950) The predominant cation inside the cells is potassium in a concentration of around 100 m equiv /Kg of cell mass magnesium and sodium are also pre sent in concentrations of 20 and 10 m equiv /Kg Cell fluid is rich in protein and these concentrations must be increased by about 50% to express them in terms of cell water rather than of total cell substance The total base in cell fluid may thus be somewhat higher than that in ECF and it is possible that some of this base is not osmotically active The greater part of cell base is balanced by phosphate but bicarbonate sulphate and chloride also contribute substantially

The acid base composition of plasma ECF and ICF is summarized in Fig 2 modified from Gamble (1947) It should be remembered that the divalent cation magnesium which makes up a definite part of cell

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base is only half as active osmotically as it is in acid base relationships so that the difference in osmolarity between ECF and ICF is exaggerated in this diagram

Measurement of electrolyte concentration in ECF and ICF gives us

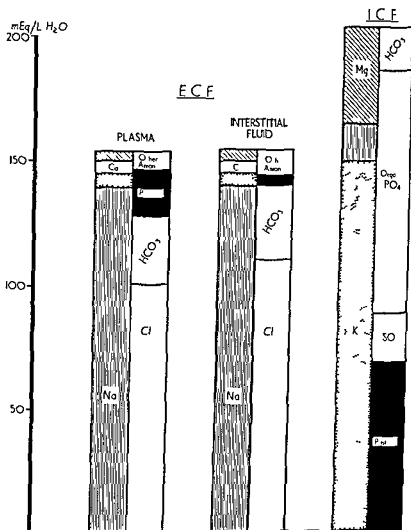


FIG 2 Balance of cations and anions in plasma interstitial fluid and intracellular fluid

a static picture of body fluid, but to appreciate the alterations in body fluid in disease we must also consider the information to be obtained from space and balance measurements The space corresponding to a given substance is determined by injecting a known amount and then determining its concentration in plasma after time for equilibrium

has been given If the amount remaining in the body is divided by the concentration we have a space or volume of distribution for that substance Spaces determined in this way may be quite meaningless when the substance in question is present in very different concentrations in different phases of body fluid On the other hand when the injected substance is limited to one compartment of body fluid its space may then be a measure of that compartment inulin and thiocyanate have been so used to measure ECF and deuterium urea and antipyrine to measure total body water In balance techniques we measure the intake and output of water itself or of the important electrolytes of body fluid and so can detect losses or gains of the substance measured over a period of time Space and balance techniques have mainly been used in experimental studies on animals and human volunteers but they have importance also in the study of disease as they can detect changes in body fluid which would not be apparent from estimations of electrolyte concentrations in plasma For example in moderate sodium deficiency the plasma sodium concentration is well within the range of normal but balance work during the relevant period shows a loss of sodium and a gain during recovery Again the serum potassium in patients with untreated diabetic coma may be raised but retention of potassium during recovery shows that they were in fact depleted of potassium

The constituents of body fluid are constantly being expended and renewed For electrolytes the general picture is intake by the alimentary tract and loss in the urine loss in sweat and faeces being very small in most cases For water the skin and lungs are important channels of excretion up to a litre a day in temperate climates and much more in the tropics The daily external turnover of water is from 1 to 3 litres of sodium from 50 to 250 m-equiv and of potassium from 50 to 150 m-equiv The kidneys adjust the urinary output to the difference between oral intake and extrarenal losses so that in health body fluid is kept reasonably constant over long periods of time although there are quite definite fluctuations from day to day above and below the mean There is also a considerable alimentary turnover of body fluid the total alimentary secretions amounting to some 8 litres per day in health this does not affect the external balance of body fluid as alimentary secretions are almost totally reabsorbed but their deviation in disease is an important cause of body fluid depletion

Causes of Body Fluid Disturbances

We shall be discussing the separate syndromes of disturbance of body fluid later but it may be well to mention the general groups of diseases in which such disturbancees are to be expected Disorders of the alimentary tract are the usual cause of depletion of body fluid Water

depletion is generally caused by a diminished intake of water due to anorexia apathy or nausea sodium and potassium depletion may be aggravated by a diminished intake of electrolyte but the primary cause is usually an abnormal loss in vomiting or diarrhoea, or in fistulous discharges and suction drainage The fluid lost in these ways may be considerably acid or alkaline, so that alkalosis or acidosis may complicate depletion of alimentary origin Gastro intestinal disease probably accounts for nine tenths of clinically important fluid depletion Next in importance to alimentary losses of water and electrolyte comes abnormal urinary loss of sodium and potassium with associated water loss this may sometimes happen in primary renal failure, but more usually when structurally intact kidneys are prevented from reabsorbing normal amounts of water and electrolyte from the glomerular filtrate Lack of adrenocortical hormones in Addison s disease acts in this way and so may any disease in which large amounts of osmotically *active non electrolyte material are being excreted by the kidneys In the* course of such an osmotic diuresis quite large amounts of water and electrolytes are lost the chief example being diabetic coma in which glucose excretion maintains a high urine volume in spite of considerable depletion of body fluid Abnormal losses of electrolyte in the urine can also be induced when large amounts of organic acids are being excreted Abnormal losses of water and electrolyte from skin and lungs may be of some importance in febrile patients and in hot climates and environments

When we turn to the causes of excess of body fluid the quantitative emphasis shifts from the alimentary tract to the kidneys Increased intake of water and electrolytes by mouth is not a primary cause of fluid excess for healthy kidneys can dispose of any alimentary load of fluid which does not provoke vomiting or diarrhoea This is not to say that when the kidneys are depressed in function by disease or posterior pituitary extract or by the excess of adrenocortical hormones which seems to characterize the post operative state then alimentary loading with water and electrolytes will still be safe It remains true however that alimentary loading with fluid is safe in comparison with parenteral fluid injection against which the body has no option of rejection Mostly however, excess of fluid in the body appears without any abnormal loading and often in spite of dietary restriction of sodium we must therefore seek its cause in a grossly impaired excretion of the constituents of body fluid Urinary suppression involves complete vulnerability to body fluid excess short of this any sustained oliguria opens the possibility of accumulation of the constituents of body fluid The important clinical syndrome is that of oedema in which sodium is primarily retained and with it enough water to expand the ECF to visible levels The kidneys normally adjust sodium output to intake

very accurately over a wide range so when sodium retention occurs on the scale found in anasarca they must be directly concerned whether as primary culprits or as victims of an inadequate supply of blood is arguable in each separate type of oedema While retention of sodium with expansion of ECF is common in disease of the heart kidneys and liver a corresponding syndrome of potassium retention with expansion of ICF has yet to be diagnosed and acute retention of water in excess of electrolyte is rather uncommon though when it occurs as water intoxication it can cause dramatic symptoms and even death anuria and post operative oliguria are the important clinical causes of water retention

After this brief survey of the groups of disease commonly associated with fluid imbalance we may now proceed to a more specific survey of the commoner syndromes of fluid imbalance These have been largely elucidated by experimental studies such as the classical work of McCance (1936) on sodium depletion clinical disorders of electrolytes usually involve multiple deficiencies and we have still much to learn about electrolyte interrelations Fortunately the regulatory mechanisms for electrolytes are generally effective so that if we can detect and correct the major electrolyte disturbance the body s own defences can often correct secondary effects This is perhaps the main practical justification for presenting an account of pure syndromes which are not often found in isolation in clinical work but it should be remembered that such an account gives only a skeleton of information and actual experience of electrolyte disorders in patients is needed to make the dry bones live

Sodium Depletion (Salt Depletion Dehydration)

The usual cause of significant sodium depletion is loss of fluid from the alimentary tract as in pyloric stenosis or severe watery diarrhoea but in diabetic coma and Addison s disease the loss of sodium is urinary in the first instance although it may later be increased by vomiting Sodium depletion exerts its effects mainly on the ECF which is reduced in volume and later in sodium concentration Both moieties of ECF are diminished in volume the plasma and the tissue ECF The fall in plasma volume is responsible for peripheral circulatory failure haemoconcentration and a diminished blood flow to the kidneys with oliguria and nitrogen retention The decrease in tissue ECF is responsible for reducing both tissue turgor and intraocular tension In severe sodium depletion in which the serum sodium level is considerably lowered the fall in osmotic pressure of ECF may allow entry of water into the cells increasing the liability to cellular overhydration and water intoxication (*vide infra*)

The clinical features associated with sodium depletion show con

siderable variation, depending on the severity of depletion the associ ated electrolyte abnormalities and the primary disease process Chronic mild sodium depletion as in the heat exhaustion syndrome causes rather indefinite asthenia malaise and tiredness, and the association of such symptoms with sodium depletion has been established only on the basis of low serum sodium levels and the ready alleviation which follows salt replacement Low levels of serum sodium are also found in *chronic disease, in which there has been no obvious channel of sodium* loss they may represent abnormal entry of sodium into tissue cells whose metabolism has been depressed by the disease process and they have little to do with symptoms these are not relieved by administra tion of salt which is in any case not retained within the body in such patients It is not safe to diagnose sodium depletion on the basis merely of a low serum sodium when there has been no obvious clinical cause of sodium depletion In more severe sodium depletion asthenia is present as in mild chronic sodium depletion but added to it we have the picture of clinical dehydration with collapsed veins low ocular tension and wrinkling of the skin Chronic wasting disease may simu late clinical dehydration quite closely but in dehydration the tissues may be perceptibly inelastic as well as wasted and there will be a his tory of fluid loss as well as of diminished food intake Most accounts of sodium depletion including that of Marriott (1947) comment on the absence of thirst which can indeed be very striking in an apparently desiccated patient but McCance described an unpleasant metallic taste in sodium depletion This may be the basis of the complaint of thirst in the minority of sodium depleted patients who not only com plain of thirst but avidly accept water in the attempt to relieve it It is perhaps too much to expect all patients to be well versed in the litera ture of their complaint or to distinguish clearly between thirst and a metallic taste There is some evidence that severe sodium deficiency may interfere with gastro intestinal motility and predispose to vomit *ing and ileus but control studies to dissociate the* effects of sodium and potassium deficiency so commonly found together have not been made Cramp is inconstant in severe sodium depletion depending probably on an excess load of water rather than on sodium depletion *per se*

The diagnosis of sodium depletion depends on the demonstration of *an adequate mechanism for sodium loss* on the clinical picture of dehydration and on supporting biochemical evidence The serum or plasma sodium potassium chloride bicarbonate and urea should be estimated in investigating disorders of body fluid but they are ancillary to a clinical assessment We have already mentioned that a low serum sodium is *not necessarily an index of sodium depletion* conversely if water intake has been restricted the serum sodium may be within the normal range in quite severe sodium depletion and in such cases a

raised blood urea in the absence of primary renal disease may be a valuable indication of sodium depletion

The treatment of sodium depletion like that of other electrolyte abnormalities involves some attention to quantitative considerations as excessive administration of sodium salts can be harmful to the patient The total amount of sodium in the body is of the order of 3000 m equiv or 70 g Mild chronic sodium depletion probably involves a sodium deficit of 200–300 m equiv and this can be very well corrected by a daily supplement of 10 g of salt added to the diet In patients with acutely established sodium depletion with clinical signs of dehydration the deficit is of the order of 500 m equiv an amount corresponding to 3 litres of normal saline These patients can be suitably treated with normal saline or with a mixture of normal saline and isotonic sodium lactate when there is significant acidosis as in diabetic coma Patients who have had long continued loss of gastro intestinal secretion with inadequate replacement can have much larger sodium deficits as much as 1500 m equiv judging by the amounts retained during recovery Such patients may do well with hypertonic saline 2% or 5% salt which relieves cellular overhydration and diminishes the quantity of fluid which has to be given intravenously (Black 1953) When large amounts of sodium have to be given about a fifth should be in the form of lactate to avoid inducing an acidosis In addition to replacing a deficit provision should be made for continuing losses of saline fluid and here again attention must be paid to the acid base composition of the fluid lost Cooke and Crowley (1952) have made a useful practical contribution here in devising fluids appropriate to the replacement respectively of gastric (acid) and intestinal (alkaline) secretions These special measures are not necessary with moderate deficits of sodium but they become important with severe sodium depletion in which the kidneys cannot be relied on to correct all the infelicities of replacement treatment Patients having intravenous sodium solutions should be examined several times daily for venous engorgement or pulmonary moisture the signs of too rapid or excessive infusion It should be remembered that for a few days after operation patients are unusually vulnerable to sodium overdosage as the urinary output of sodium is greatly depressed (Moore and Ball 1952)

Sodium Excess (Oedema)

We have already stressed the importance of diminished output of sodium and the relative irrelevance of increased intake in promoting sodium excess other than acute overdosage of salt by infusion Oedema in association with primary renal disease is dealt with in the chapter on renal disease the commonest forms of oedema are those in which the kidney is structurally sound but is the victim of misdirection retaining

sodium in spite of a considerable excess of sodium in the body Several mechanisms have been demonstrated by which sodium retention by the kidneys can be induced A fall in cardiac output with associated fall in renal blood flow and glomerular filtration rate (GFR) will reduce the filtered load of sodium and so favour diminished excretion The relevance of this has been extended by the demonstration that even in high output types of heart failure such as chronic cor pulmonale, the renal blood flow may be less than normal (Davies and Kilpatrick 1951) It has also been shown that an increase in renal vein pressure *diminishes sodium output but the effect is transient* even when a high renal vein pressure is maintained Even when allowance is made for a fall in GFR the excretion of sodium in oedema is abnormally low indicating an increased tubular reabsorption of sodium The main cause of this is an increase in the activity of salt retaining adrenal steroids and an excessive output of aldosterone has now been demonstrated in oedema of cardiac hepatic and renal origin (Luetscher and Curtis 1955) Increased output of antidiuretic substances has also been shown but this is inadequate to explain sodium retention as pituitary ADH does not significantly affect sodium output The mechanisms responsible for the different types of oedema are often multiple as was *stressed by Starling in 1909 the intervening years have increased the* number of sodium retaining mechanisms known to us but an assessment of their relative importance for example in cardiac oedema is still controversial We cannot here consider the special measures appropriate to individual types of oedema but can deal only with those measures of restricting sodium intake and increasing sodium loss which are commonly used in all forms of generalized oedema

Restriction of Sodium Intake When salt is omitted in cooking and at table the salt content of an ordinary diet falls to about 3 g /day most of which is in bread When salt free bread is substituted for ordinary bread the daily intake of salt is about a gram Special diets such as the *rice diet contain less than a quarter of a gram of salt per day,* but they are monotonous and can be adhered to only in an atmosphere of unrestrained therapeutic enthusiasm on the part of doctor and patient Unfortunately the excretion of salt by oedematous patients is seldom as much as a gram per day so dietary sodium restriction must be rigorous if any real effect is to be obtained by this means It is however possible to give a less restricted diet if the sodium contained in it is covered by a cation exchange resin These resins can take up about 1 m equiv of sodium per gram of resin in exchange for the cation with which the resin has previously been loaded ammonium and potassium can be used as exchangeable cations and often a mixture of ammonium and potassium loaded resin is given in divided doses to a total of 50–100 g /day Ammonium resins are acidifying in their effect while

the dosage of potassium must be limited when there is any renal excretory failure If a diet without added salt but including ordinary bread is given with 50 g of resin, the effective sodium intake is of the same order as with a rice diet but there is a tendency to acidosis in so far as the resin given is charged with ammonium This is not necessarily harmful but it calls for biochemical control A regime of sodium restriction is certainly effective in preventing increase of oedema but the body responds to it by actively conserving sodium so by itself it may not make any dramatic contribution to getting rid of oedema fluid for which purpose a forced loss of sodium from the body must be induced

Promotion of Sodium Loss Leaving aside direct removal of oedema fluid by paracentesis or Southey s tubes the most effective means of ridding the body of sodium in responsive patients is diuresis in comparison with which diaphoretic and purgative drugs are ineffective The drugs of established efficiency are the organic mercurials and trials have also been made with carbonic anhydrase inhibitors analogous to sulphanilamide both these groups depress renal tubular reabsorption of sodium so that a greater proportion of the filtered load of sodium is excreted They do not influence the filtered load of sodium directly but are much more efficient than the xanthine diuretics which affect filtration rate and can be used as adjuvants It is likely that the primary action of mercurials is on chloride reabsorption sodium being excreted as an accompanying cation the Cl Na ratio in urine excreted under the influence of mercurials is appreciably higher than the Cl Na ratio in plasma and ECF Repeated mercurial diuresis may thus lead to chloride depletion in excess of sodium and this change is associated with a lessened diuretic response The effect of ammonium chloride in correcting chloride depletion may be the basis of its well established potentiation of mercurial diuresis The carbonic anhydrase inhibitors unlike the mercurials diminish urinary acidity and it may be that alternation of mercurial and sulphanilamide diuretics will avoid significant acidosis or alkalosis during induced renal elimination of sodium

Resistance to Mercurials, and 'Low Salt' Syndromes While many patients have their lives prolonged and perhaps more important their discomfort diminished by mercurial diuretics a stage is often reached at which the diuretic response to mercurials becomes less and less effective At this stage the serum sodium is often found to be markedly decreased and there may also be clinical evidence of a diminished blood volume persistent oliguria and symptoms generally associated with sodium depletion—this in spite of persistent peripheral oedema This state of affairs often associated with a rising blood urea generally carries a bad prognosis and usually denotes circulatory inefficiency so extreme that fluid can no longer be mobilized from the tissues to restore

diabetic coma Retention of potassium during recovery analysis of red cells and muscle biopsy material and determination of exchangeable potassium in the body with isotopes have all been used in the study of potassium depletion but do not yet give easily interpreted results A low plasma concentration of potassium is very suggestive of depletion but the normal range is somewhat wide and values falling within it certainly do not rigorously exclude potassium deficit An unexplained rise in plasma bicarbonate is suggestive of potassium depletion which is often associated with hypochloraemic alkalosis in ECF In the ab sence of renal disease a low urinary K output suggests K depletion especially if it persists after giving potassium on the other hand with primary renal disease and also when long standing K depletion has damaged the kidneys the urinary output of K may be quite high even at low concentrations of K in the plasma There is in fact no bio *chemical test for potassium depletion which invariably gives a rapid* and correct result and diagnosis has often to be based on knowledge of the circumstances which have led up to the present clinical state

The treatment of potassium depletion is complicated by the dangers attending too rapid entry of potassium into the extracellular compart ment especially when renal excretion of potassium is impaired by oliguria The problem is much simpler when there is no vomiting as oral administration of potassium is most un likely to cause toxic effects Potassium chloride can be given in 2 g doses well diluted with fruit juice or water every four or six hours when potassium deficiency is complicated by acidosis a mixture of 1 g each of potassium bicarbonate acetate and citrate in 8 ml of water can be given four times a day in fruit juice When there is oliguria even oral ad ministration of potassium should be controlled by estimations of the serum level or serial ECGs When potassium cannot be given by mouth and there is good clinical evidence of significant potassium depletion such as hypo kalaemic paralysis of muscle or paralytic ileus the intravenous infusions used to correct de hydration should also contain potassium as soon as urine output has been restored to a reasonable level Potassium concentration in *such infusions should not exceed* 40m equiv /L and the rate of infusion should not exceed a litre in three hours the rate of infusion must be supervised and frequent estimations of serum potas sium or ECG recordings made On the other hand infusions such as

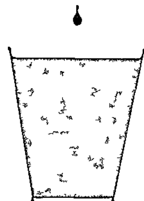


FIG 3 A drop in the bucket Rat o of total potassium in one l tre of Hartmann s solut on to total potass um in the intracellular fluid of a normal man (*Smart G A in Progress in Cl n cal Med c ne Chu ch ll*)

Hartmann s solution with a potassium concentration of 5 m-equiv /L can make no effective contribution to potassium replacement as is graphically demonstrated in Fig 3 When the patient is well enough to take a mixed diet potassium salts may be discontinued unless a persist ing low serum potassium or other evidence of potassium deficit makes it advisable to continue oral potassium indefinitely

Potassium Excess

As a spontaneous syndrome this has been observed in Addison s disease and in renal failure including acute tubular necrosis It can also happen as the result of excessive potassium administration either as potassium citrate in the symptomatic treatment of urinary infection or in the course of correcting potassium depletion As with potassium depletion the most clearly demonstrated effects are those determined by alteration of the potassium concentration in ECF As the plasma potassium level approaches 8–10 m equiv /L cardiac arrhythmia and changes in the electrocardiogram give some warning of cardiac arrest in diastole In contrast to hypokalaemia in which the T wave is in verted and the QT interval prolonged the ECG with rise in plasma potassium shows first peaking of the T wave then widening of the QRS segment and loss of P waves tending towards a biphasic tracing (Darrow 1950) The other notable manifestation of hyperkalaemia is muscular paralysis sometimes of an ascending Landry type associated with paraesthesiae which leads Bull *et al* (1953) to regard it as an acute peripheral neuropathy rather than an interference with myoneural transmission There is not a close relationship between the extent of paralysis and the exact level of plasma potassium and in one patient Bull and his colleagues noted a tendency for paralysis to recur at pro gressively lower concentrations of plasma potassium Nothing definite is known of the effects of increased cellular potassium although las situde and confusion have been attributed to this

Since the dangers of excessive potassium are mediated by a raised concentration in ECF treatment directed to lowering this may be effective even if it does not eliminate potassium from the body Intra venous injection of 50 g of glucose with 50 units of soluble insulin withdraws potassium into the cells and has been observed to ameliorate the symptoms of hyperkalaemia The effect is transient and measures should also be taken to withdraw potassium from the body Correction of sodium depletion is important as it expands the ECF and so lowers the potassium concentration therein and also promotes urinary loss of potassium in saline diuresis Potassium can also be withdrawn from the body by giving cation exchange resins charged with ammonium or sodium 50–100 g daily by mouth this method is particularly useful when large saline infusions are contra indicated as in anuria

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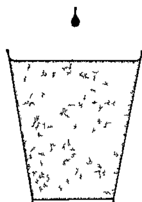


FIG 3 A drop in the bucket Ratio of total potassium in one litre of Hartmann's solution to total potassium in the intracellular fluid of a normal man (*Smart G A in Progress in Clinical Medicine Churchill*)

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Water Depletion

This syndrome arises when water is not available in adequate amount or when intake is restricted by coma or inability to swallow and retain fluid An adequate amount cannot be concisely defined for extra renal losses of water may be increased by fever and thermal sweating while renal losses of water are increased in osmotic diuresis renal failure and diabetes insipidus Certainly any intake less than a litre a day is inadequate when urine is being formed but the adequate amount for a given patient may greatly exceed this When the intake of water falls below the output and there is no concomitant loss of electrolyte

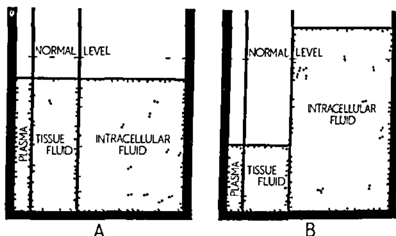


Fig 4 Relative changes in the volumes of the fluid-compartments in (A) water depletion and (B) sodium depletion (Modified from Marriott 1947)

the osmotic pressure of body fluid inevitably increases the first impact of this is no doubt on the ECF but water is then withdrawn from the cells and in the end the water deficit is pretty fairly divided between the two compartments

The participation of ICF in the fluid loss explains many of the differences between water depletion and depletion of sodium in which the fluid loss falls quite disproportionately on the ECF Circulatory impairment is absent in moderate water depletion and kidney function remains surprisingly adequate in spite of oliguria the urine formed being highly concentrated For the same degree of body fluid deficit, water depletion causes less clinical dehydration than does sodium depletion On the other hand thirst—which is absent or equivocal in sodium depletion—is raging in water depletion Haemoconcentration is absent in water depletion and the veins are not collapsed The clinical differences between water and salt depletion can largely be

explained in terms of their very different impact on the body fluid compartments represented schematically in Fig 4 Recognition of water depletion is based on evidence of defective water intake great thirst scanty urine of high specific gravity absence of notable circulatory impairment and a raised plasma sodium level

Treatment of water depletion involves the supply of water to the body in amount sufficient to repair the deficit and to cover continuing losses of water For practical purposes satisfaction of thirst and repair of a water deficit can be equated so that a conscious patient who has strayed into water depletion can be allowed to treat himself as soon as he can absorb water In patients who cannot drink water can be given by slow rectal drip or intravenously For intravenous use 5% glucose must be used and this is probably preferable for rectal use also because patients who cannot take water by mouth will also be starving and carbohydrate considerably decreases the rate of breakdown of body protein For maintenance of the comatose patient 2 litres of 5% glucose per day provides enough water to replace losses and also 100 g of carbohydrate which is enough to exert a maximal protein sparing effect Larger amounts of water should be given to patients who are thirsty and can be presumed to have a water deficit in addition to their water needs for maintenance but in patients who are not thirsty water intake should be restricted to 2 litres per day In pure water depletion electrolytes should not be given as they must either carry off water in the urine or increase the rise in osmotic pressure of body fluid

Water Excess (Water intoxication) (Wynn and Rob 1954)

Patients do not voluntarily take water in excess of their needs so this syndrome is almost always the consequence of therapeutic zeal It has been reported mostly in patients with anuria or after operation when the renal defence against a water load is absent or imperfect but it has also been described in association with lavish colonic wash outs Judging largely from experimental work the essential feature of water intoxication is a fall in the osmotic pressure of body fluid so that sodium depletion predisposes strongly to water intoxication which may then occur without there being an absolute excess of water in the body As just indicated the other important precursor of water intoxication is any constraint on water diuresis Occasionally great pertinacity on the part of doctors or nurses will induce a patient to commit water intoxication by drinking in spite of his growing aversion to water much more often parenteral or rectal administration has been responsible Headache lethargy muscular cramps and a disinclination to drink are early symptoms of excessive loading with water later come retching muscle twitching and generalized convulsions and the patient may die if his disorder be not recognized and treated Water

intoxication should not occur with temperate fluid therapy, but if it does, mild symptoms can be treated by withdrawing water and encouraging sweating convulsions should be treated by intravenous injection of 50 ml of 10% saline

The disturbances with which we have dealt till now those of sodium potassium and water have had at least two claims to simplicity—the substances involved are clearly defined chemically and except for water they are neither created nor destroyed in the body The disturbances of acid base balance are complicated by the multiplicity of anions involved and by the emergence of both acidic and basic ions from non electrolyte precursors in the course of metabolism We must meet this challenge with an even more vigorous suppression of detail though conscious that omissions which at present seem permissible may in the near future be made blameworthy by the advance of knowledge but a writer on body fluid must accustom himself to being always out of date in some quite important matters

Acidosis

The normal course of metabolism produces very large amounts of acid in the body but by far the greater part of this—as much as 20 moles per day—is carbonic acid derived from carbon dioxide and again dissociating to carbon dioxide and water in the lungs This volatile acid is excreted by the lungs and only negligible amounts of bicarbonate are excreted by the kidneys so long as the urine is acid The kidneys are not however without influence on the carbonic acid bicarbonate buffer system as they regulate the cation which is available to form bicarbonate Mainly however, the kidneys have to deal with the non volatile anions present in the diet—mainly chloride—or formed in intermediate metabolism—phosphate and sulphate from protein phosphate and keto acids from phospholipids and fatty acids and any overspill of organic acids from the general metabolic pool These anions formed in metabolism are partly neutralized by available cation ingested in the food but on our usual acid ash diet fixed anion is formed in excess of available cation to the amount of 50–100 m equiv / day There is therefore even in normal metabolism an inherent tendency to acidosis which is kept in check by respiratory elimination of carbon dioxide and renal elimination of fixed anion In eliminating the excess of fixed anion formed in metabolism the renal tubules economize fixed cation by exchanging it for hydrogen and ammonium ions the economy of fixed cation being represented quantitatively by the sum of ammonia and titratable acid excretion

The normal defence of the body against acidosis is vulnerable at several points and these correspond to different modes of origin of pathological acidosis—metabolic renal and respiratory The defence

mechanism may be swamped by overproduction of metabolic anion—e g the ketosis of starvation or uncontrolled diabetes or the increased formation of phosphate and sulphate in accelerated protein catabolism The same effect of an increased metabolic load of anion may be produced artificially by the ingestion of fixed anions of resins charged with hydrogen or ammonium ion or of ammonium and calcium chloride in which the cation is converted to urea or taken up into bone leaving the chloride anion as a charge on acid excretion Yet again metabolic acidosis can be produced by loss of cation from the body in excess of anion the usual vehicle of such loss being the alkaline pancreatic and intestinal secretions in watery motions Renal acidosis arises when the kidneys lose their power to elaborate an acid urine and this may happen either in association with or divorced from renal excretory failure this type of acidosis will be more fully considered in the chapter on renal disease Respiratory acidosis is the results of defective elimination of carbon dioxide by the lungs as in chronic emphysema The carbonic acid content of the blood rises and with it the plasma bicarbonate in order to maintain the $BHCO_3$ $H HCO_3$ ratio on which plasma pH depends In the metabolic and renal types of acidosis there is an excess of fixed anion in the blood and carbonic acid is displaced from combination with cation the excess carbonic acid is eliminated by overbreathing leaving the $BHCO_3$ $H HCO_3$ ratio comparatively little diminished but at a reduced level of plasma bicarbonate There should not be any clinical confusion between respiratory acidosis and metabolic or renal acidosis but their opposite effects on the plasma bicarbonate may confirm the distinction Metabolic and renal acidosis may be distinguished biochemically by the very acid urine of metabolic acidosis in contrast to the feebly acid neutral or even alkaline urine found in renal acidosis Greater precision can be given to this distinction by observing the acidity of the urine after a 3 g dose of ammonium chloride but this is not indicated when the plasma bicarbonate is already low enough to suggest an adequate stimulus to urine acidification

Biochemically demonstrable acidosis of short duration may not cause any symptoms In severe metabolic or renal acidosis hyperpnoea may be very obvious and the overventilation without great distress should be distinguished from the ineffective dyspnoea of respiratory acidosis Chronic renal acidosis even though not attended by detectable hyperpnoea can give rise to symptoms related to the depletion of body cation in addition to sodium and potassium depletion loss of calcium will in time lead to osteomalacia with bone pain and pseudo fractures The treatment of acidosis varies with its origin severity and chronicity Specific treatment for the disease process leading to acidosis must be given when available this is likely to be most helpful in metabolic acid

osis in which arrest of cation loss or anion production can sometimes be achieved by specific treatment such as sulphaguanidine in dysentery or insulin in diabetic ketosis Respiratory and renal acidosis are more likely to be caused by irreversible processes and treatment of the acidosis itself may be needed Acute acidosis can be treated by oral sodium bicarbonate in a dosage of 2 g repeated 2 or 4 hourly under biochemical control In patients who may vomit intravenous sodium lactate may be given this is usually supplied in 40 ml ampoules of molar sodium lactate and this should generally be diluted with distilled water to 1 6 molar concentration which is isotonic with plasma When acidosis is associated with severe sodium depletion molar sodium lactate can be given undiluted on the same general indications as hypertonic saline Intravenous use of lactate should be controlled by frequent determinations of the plasma bicarbonate, as formulae to predict the dose of lactate are not reliable Chronic renal acidosis associated with osteomalacia should be treated by regular alkali administration in addition to calcium salts and calciferol Albright s alkalinizing citrate mixture is a convenient way of doing this His original solution contained 140 g of citric acid and 98 g of sodium citrate per litre and was given in a dose of 50–150 ml /day in divided doses In view of associated potassium depletion Milne *et al* (1952) have recommended 75 g of sodium citrate and 25 g of potassium citrate in place of the 98 g of sodium citrate in the original mixture All these treatments have as their basis the addition of cation to the body to neutralize the excess of anions unfortunately they cannot be applied in respiratory acidosis in which the base content of the body is already normal or even increased by oedema Another limitation on direct therapy of acidosis may be imposed by calcium depletion in relation to tetany, acidosis increases the proportion of plasma calcium which is ionized and correction of acidosis may have to be abandoned because of the appearance of tetany

Alkalosis

Since the general trend of both normal and abnormal metabolism is towards production of acid in excess of base and continuous secretion of acid must go on to maintain the normal slightly alkaline reaction of body fluid pathological increase in the alkalinity of body fluids is somewhat uncommon Excessive ingestion of alkalis usually in the self medication of patients with peptic ulcer and loss of acid in vomitus notably in pyloric stenosis are both causes of metabolic alkalosis Hyperventilation in hot baths at high altitudes and in attacks o hysterical over breathing may lead to respiratory alkalosis It is doubtful if a syndrome exists which is the precise converse of renal acidosis since renal failure normally leads to acidosis but abnormal kidney

function probably plays some part in the alkalosis of ECF which often complicates potassium depletion (Orloff *et al* 1953) Acute respiratory alkalosis causes over breathing tetany and there is some evidence that many of the symptoms of psychoneurotic illness may be based on hyperventilation Such patients may be improved by explanation of the nature of their symptoms especially if an attack can be induced by voluntary over breathing and terminated by re breathing from a paper bag (Lewis 1954) The metabolic alkalosis complicating peptic ulceration may be suspected when the patient shows mental confusion and apathy or the carpopedal spasm of latent tetany more often it comes to light when the plasma bicarbonate is measured because of a history of alkali ingestion or persistent vomiting Although massive amounts of milk and alkalis can be given for a few weeks without apparent harm many patients have now been described with alkalosis after long standing ingestion of milk and alkalis this syndrome may improve with cessation of the alkali medication but renal damage with calcification may progress to renal failure In patients with pyloric stenosis the plasma often shows an alkalosis this may disappear when the patients are rehydrated and given chloride or it may need potassium salts for its correction (Davies *et al* 1956)

We have now completed a brief survey of the various syndromes into which disturbances of water and electrolyte can be analysed but in clinical practice these are of course combined in varying degree in different patients If we take pyloric stenosis as an example the pre dominant disturbances are sodium depletion and alkalosis and as a practical treatment in preparing the patient for operation the intra venous infusion of isotonic sodium chloride solution has often shown itself to be thoroughly effective In addition to these obvious dis turbances there are other factors which can usually be neglected for practical purposes but which may on occasion make a different plan of treatment desirable A patient who has accustomed himself to high dosage of sodium bicarbonate may show little evidence of sodium depletion but may still have a considerable alkalosis these patients often have significant potassium depletion since the vomited material contains potassium as well as sodium and if sodium is being replaced by sodium bicarbonate dehydration may be postponed for long enough to allow potassium depletion to develop These patients in whom alkalosis predominates over dehydration may respond well to potassium chloride in small doses by mouth and not require intra venous saline On the other hand when pyloric stenosis develops rapidly and is associated with loss of appetite and vomiting of all food sodium depletion appears rapidly and the alkalosis from loss of gastric acid is counteracted by the acidosis of starvation the clinical and biochemical picture may then be one of sodium depletion without much

alkalosis In most cases intravenous sodium chloride is the mainstay of treatment, and potassium chloride should also be given by mouth in divided doses When the patient *is operated on his losses of sodium* by vomiting cease abruptly and at the same time his urinary sodium output drops very sharply, while the potassium output in urine rises At this time, saline infusions should be *discontinued but the oral* potassium should be maintained persistence with intravenous saline at this stage especially in the presence of uncorrected potassium deficiency carries quite a definite risk of peripheral and *more important* pulmonary oedema The intake even of water should be restricted for a day or two after operation as the urine volume is low and does not increase in response to a water load

In the practical management of electrolyte disorders a grasp of principle has to be supplemented by considerable attention to detail if the most effective treatment is to be given The significant details are by no means always those which are revealed by chemical estimations and on occasion these may even be misleading When a patient is clinically dehydrated the correction of sodium depletion seems to me the first step in treatment for errors in fluid therapy which are serious in patients with functional renal failure can often become trivial when the kidneys have been restored to normal efficiency by improving their circulation and such errors have to be reckoned with since our knowledge of body fluid abnormalities is incomplete in many respects The best general policy is to treat well established depletions especially of sodium vigorously but to be cautious in fluid administration where no depletion has been demonstrated I have refrained from giving hard and fast quantitative directions for fluid therapy as I am sure they do more harm than good and therapy should be guided largely by the progress which is being made

The main thesis implicit in this presentation has been that it is expedient to recognize the predominant abnormality *in body fluid* and to apply treatment specifically directed to its correction It is only fair to state however that this thesis though widely supported does not commend *itself to all who have extensive experience* of fluid therapy Talbot Crawford and Butler (1953) have reported their use of a general electrolyte replacement solution which in their view is suitable for all *distortions of* body fluid and serves both as a replacement and as a maintenance solution This solution has the composition

Sodium	40 m equiv /L
Potassium	35 5
Chloride	40
Lactate	20
Phosphate	15 5
Dextrose	3, 5 or 10 %

They express the dose in litres/sq metre of surface area/day to assist its application to paediatric problems For maintenance 2 litres/sq m /day is adequate but for replacement amounts up to 3 5 litres/sq m /day may be given They indicate however that when there is severe circulatory and renal impairment due to sodium depletion this should first be corrected and claim this can be done in 1–2 hours by giving at a rate of 8 ml /sq m /min a solution of 0 51% sodium chloride in 5% dextrose Their general replacement solution is so planned as to fall within the normal range of possible excretion of its constituents and for that very reason I would doubt its adequacy in the very severe alimentary depletions of sodium and potassium which can be encountered There would also seem to be a risk of cellular overhydration with this regime in really severe sodium depletion For moderate deficiencies the obvious convenience of their method makes it seem worthy of extended trial An important contribution on more orthodox lines to the treatment of dehydration in infants is the 1952 Medical Research Council memorandum (No 26) on 'The treatment of acute dehydration in infants

ILLUSTRATIVE CASE REPORT

A man of 25 had had intermittent dyspepsia for ten years with little response to medical treatment On 2 9 52 he had an anterior Polya partial gastrectomy and on 8 9 52 severe generalized abdominal pain led to a further laparotomy at which the duodenal stump was found to be leaking A duodenal fistula established itself and large amounts of fluid drained from it which were only incompletely replaced by blood and saline infusions His general condition deteriorated and he was transferred to Manchester Royal Infirmary on 10 10 52 He was then both wasted and dehydrated with wrinkling of the skin dry tongue low intraocular tension and shrinkage of the orbital tissues producing the appearance of exophthalmos His blood pressure was 100/60 peripheral circulation was poor and the superficial veins were collapsed A small sample of blood showed haemoconcentration and the serum sodium was 118 m equiv /L and potassium 5 4 m equiv /L There was not enough blood for chloride and bicarbonate estimation but the fistulous fluid was alkaline (pH 8) and contained sodium 96 m equiv /L and potassium 4 8 m-equiv /L There was thus clinical and biochemical evidence of a severe sodium depletion though there was no direct biochemical evidence on the acid base balance in plasma it was assumed that there would be considerable acidosis in view of the long-continued loss of alkaline fluid Although the serum potassium level was normal potassium had been lost in the fistulous discharge and it was thought wise to cover the period of sodium replacement with expansion of extracellular fluid by giving potassium salts by mouth It was also decided to collect the fistulous discharge and to return it to the intestine by tube

A mixture of equal parts by weight of potassium acetate bicarbonate and citrate (1 g of each in 8 ml of water) was given in fruit juice (1 teaspoonful

4 hourly) During 24 hours twelve 40 ml ampoules of molar sodium lactate and 2 pints of 5 % saline were infused intravenously The earlier part of this infusion was mainly lactate to correct the acidosis fairly quickly After this infusion he was much better and his dehydration had been largely corrected The serum sodium was then 130 m-equiv /L potassium 2 8 m equiv /L chloride 94 m equiv /L and bicarbonate 26 7 m equiv /L The fall in the serum potassium during correction of a massive sodium deficit and in spite of oral potassium is noteworthy and also the large amount of sodium which was given without restoring the serum sodium level completely to normal The oral potassium mixture was continued and salt was added to the patient s drinks to a concentration of around 0 5 % in view of the remaining sodium deficit There was further improvement the fistula had closed spontaneously on 2 11 52 and the patient was discharged to convalescence on 5 11 52

Comment

This report illustrates the use of hypertonic sodium solutions in the repair of a massive sodium deficit Hypertonic saline should be given only when the clinical evidence of a large sodium deficit is confirmed by a definite lowering of serum sodium The massive infusion should contain lactate as well as chloride to prevent acidosis and it should be covered by oral potassium Another point of interest is that the positive fluid balance in this patient (and in others) was less than would be required to dilute the infusion down to isotonicity, suggesting that water came from the cells in significant amount there may be less danger of producing damp lungs with hypertonic infusions in that no excess of water is being given

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ALDOSTERONE AND ALDOSTERONISM

It has been known for some years that a substance or substances capable of inducing salt retention on injection into animals was present in human urine especially in the urine of oedematous patients but Simpson Tait and Bush (1952) were able to show that almost all this salt retaining activity was attributable to a single steroid substance which has since been demonstrated in adrenal vein blood isolated from adrenal tissue synthesized in small amount and defined chemically This steroid at first called electrocortin but now known as aldosterone promotes retention of sodium and chloride and enhances the excretion of potassium It is much less certainly under pituitary control than are the glucocorticoids and in some species which may include man it is formed in the superficial zona glomerulosa of the adrenal and not like the glucocorticoids in the deeper layers Secretion of aldosterone has been stimulated experimentally by restricting sodium intake by lowering the volume of plasma or ECF and by raising the potassium

intake and aldosterone output has been suppressed by the converse procedures

The salt wasting of Addison s disease can be related to deficiency of aldosterone Total adrenalectomy prevents the formation of aldosterone whereas in panhypopituitarism the urinary output of aldosterone is not reduced Even the information so far available on aldosterone warrants the expectation that a primary deficiency of aldosterone is possible without the deficiency of glucocorticoids which is equally present in Addison s disease and a patient has already been observed by Relman and Schwartz in Boston, who probably exemplifies primary hypoaldosteronism This man presented with hyperkalaemia associated with episodic cardiac arrest and was found to have no aldosterone de tectable in the urine but a normal output of 17 hydroxycorticoids

Excessive excretion of aldosterone has now been observed in renal hepatic and cardiac oedema and an excessive production of aldosterone is the major factor if not the only one which determines the abnormal reabsorption of sodium and chloride by the renal tubules in these patients It would account entirely for the sodium retention in these patients with oedema in whom glomerular filtration is not impaired and even in cardiac oedema where lowered GFR is important exces sive tubular reabsorption of sodium and chloride is also present The stimulus to this very common type of secondary aldosteronism has not been fully established therapeutic sodium restriction fall in cardiac output diminished plasma volume from hypoproteinaemia or dimin ished perfusion of a volume receptor are some of the possible agencies The importance of sodium restriction is emphasized by the observation that large amounts of aldosterone have been found in the urine of patients with sodium losing pyelonephritis

A syndrome of primary aldosteronism was described by Conn (1955) and a number of other patients have since been reported These patients show a severe potassium depletion and retention of sodium leading to hypernatraemia but not commonly to oedema there is hypertension and often renal damage with failure of urine concentration An adrenal tumour may be demonstrated by tomography with or without pre sacral air insufflation but some of the tumours have been very small yet clearly responsible for the syndrome because of the regression of symptoms which has followed their removal A few patients have also been reported in whom increased output of aldosterone has been associated with episodic oedema and not with potassium deficiency, but here it is difficult to exclude all causes of secondary aldosteronism and it is not yet certain that this represents a second syndrome of primary aldosteronism It has recently been reported that an increased excretion of aldosterone preceded the paralytic episodes in two patients with familial periodic paralysis (Conn *et al* 1957) So far the most

certain expression of primary aldosteronism is the type with predominant potassium deficiency since primary renal disease can lead to potassium deficiency and also to sodium deficiency with secondary aldosteronism the precise diagnosis in the individual patient may be difficult A useful discussion of the diagnostic problems involved has appeared recently (Mahler and Stanbury 1956) in some patients surgical exploration of the adrenals may be needed to exclude tumour

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CHAPTER 3

METABOLIC ASPECTS OF RENAL DISEASE

D A K BLACK

IN order to appreciate the varied impact of renal disease on metabolism we must keep in mind the astonishing versatility of function displayed by the kidneys in health We cannot here concern ourselves with the detailed mechanisms of renal function except in so far as they are directly concerned in specific metabolic defects found in renal disease any such attempt has been made quite redundant by Homer Smith s treatise on *The Kidney* (Smith 1951) in which the evidence for our current concepts of renal function is given at length Ludwig s view that Bowman s capsule is a filtering device to produce a plasma ultra filtrate containing only traces of protein has been supported by the micro puncture studies of Richards and measurement of the rate of formation of glomerular filtrate (GFR) has been achieved by Smith s own method of the clearance rate of inulin The volume of glomerular filtrate is about 120 ml per minute in man whereas the volume of urine is very much smaller from a fraction of a millilitre up to 15–20 ml /min It is clear from this that in general, reabsorptive processes in the tubule must preponderate over secretory processes but a pure filtration reabsorption theory of the type proposed by Cushny is now untenable especially in its original form of a reabsorbate of the com position of ideal plasma an apparently simple hypothesis which would in fact require operations of great complexity on the individual constituents of the reabsorbate and which would have to be elaborated from a tubular fluid of varying composition

Many substances such as sodium chloride water phosphate glucose and uric acid appear in the urine in amounts which are small com pared with those originally filtered and in respect of these substances reabsorption must be the paramount activity of the tubules and twenty years ago renal physiologists with few exceptions had quite abandoned Heidenhain s hypothesis of tubular secretion as an important factor in urine formation However substances were discovered which had a clearance rate in excess of that of inulin implying that they were being excreted more rapidly than they were being filtered in the glomerulus Tubular secretion was first demonstrated for substances foreign to the body, such as phenol red diodone and *p* aminohippurate some of

these are completely cleared from plasma perfusing the tubules and this has become the basis of methods for measuring renal plasma flow (Smith 1951) More recently secretion has been demonstrated for normal body constituents including potassium urobilin and hydrogen ions It has become apparent in fact that the tubule cells have distinctive patterns of behaviour for the different substances exposed to them either in tubule fluid or in the plasma In addition to excreting waste products such as urea the kidneys deal with other substances such as water and electrolytes in a way that maintains their amount or concentration within the body relatively constant in spite of variation in dietary intake or extrarenal loss Cannon has described this type of renal action as homoeostatic in contrast to the rather indiscriminate excretory action on urea or creatinine From the clinical point of view the shift in emphasis from excretory to homoeostatic function of the kidney has clarified some problems of pathogenesis and has altered our outlook on treatment in some respects Before discussing the syndromes of disordered renal function we must however review very briefly the normal renal handling of those urinary constituents whose abnormal handling in different types of renal disease can constitute a threat to the body s economy

Water

Micro puncture studies suggest that in the proximal part of the renal tubule the filtrate is reduced to a sixth of its original volume but that its total concentration is not appreciably altered in spite of changes in composition due to the retention of most of the filtered urea and the reabsorption of sodium and associated anions at a rate somewhat greater than that of water A process of proximal isosmotic reabsorption can clearly make no contribution to changing the osmolarity of body fluids and if such a process is accepted we must look to the distal tubule for what Homer Smith has called the facultative reabsorption of water in contrast to the more or less obligatory reabsorption of water along with solutes in the proximal tubule A sufficient volume of water—about 20 ml /min —is delivered to the distal tubule to cover the full range of variation observed in urine volume When body fluids are hypertonic pituitary antidiuretic hormone (ADH) permits maximal reabsorption of water in the distal tubule without directly affecting the absorption of solutes and small amounts of concentrated urine are then formed When body fluids are hypotonic ADH action on the distal tubule is suppressed and the urine is copious and dilute The ADH mechanism is the predominant regulator of urine volume but this can also be modified by the load of total solutes delivered to the distal tubule and by the action of adrenal steroids of the cortisone

group * Although the transition from oliguria to full water diuresis can be induced by water drinking without any detectable change in GFR primary changes in GFR could influence urine flow by altering the total amount of solutes delivered to the distal tubule, the solute load can also be altered by change in the plasma level of osmotically active substances such as mannitol glucose or saline This results in osmotic *diuresis, which differs from water diuresis in that the increase in urine* volume is accompanied by an increased rate *of solute output This* distinction has clinical relevance, in that the sustained water diuresis of diabetes insipidus does not lead to depletion of body solutes whereas osmotic diuresis caused *by glucose or urea can lead to significant elec* trolyte depletion It is not known whether adrenal corticoids influence urine volume under normal circumstances but the failure of water diuresis *in Addison s disease and Simmonds s disease shows that their* absence prevents adequate inhibition of water reabsorption by the renal tubules

Sodium

Only about 1–2% of the sodium filtered at the glomerulus is normally *excreted and at the height of a mercurial diuresis the percentage of* sodium excreted is only about 15% whereas in quite moderate sodium depletion only 0 1% of filtered sodium is excreted Some similarity in *the renal handling of sodium and of water is indeed to be expected in* the interests of extracellular fluid (ECF) homoeostasis and there is considerable evidence, summarized by Smith (1951) to support a *somewhat obligatory reabsorption of sodium in the proximal tubule* and a regulated reabsorption of a 15% moiety of filtered sodium in the distal tubule Smith has suggested that there is an upper limit to the *reabsorptive capacity of the distal tubule for sodium so that at high* GFR or plasma sodium level some sodium is excreted whereas lower ing of GFR or plasma sodium level leads to virtually complete distal *reabsorption of sodium and a sodium free urine This theory would* account for responsiveness of sodium excretion not only to plasma sodium concentration but also to change in the volume of ECF or at *least of plasma There is increasing evidence however, that* change in filtered load of sodium is not the sole determinant of sodium excretion but that tubular behaviour to a given load of sodium may be of critical *importance For example, the very low sodium excretion in mild* sodium depletion cannot be fully explained by changes in filtered load of

* There is now convincing evidence (Berliner and Davidson 1957) that a hypertonic urine can be formed independently of ADH action when the amount of filtered water and solutes is reduced this mechanism of free water absorption is probably in the collecting *tubules distal* to the site of ADH action (Wirz, 1957) This mechanism could account for the hypertonic urine which can be formed by severely dehydrated patients with diabetes insipidus and also for the concentrated urine which is formed by some patients with cardiac failure in spite of *hyponatraemia*

sodium and on the other hand patients with Addison s disease lose sodium in the urine even at reduced levels of GFR and plasma sodium In other words the reabsorptive capacity of the tubules for sodium is not a fixed thing but can be modified certainly by adrenal corticoids and probably in other ways as well Under most circumstances sodium and chloride ions are excreted in the urine in equivalent amounts implying that sodium reabsorption is appreciably greater than that of chloride as the Na Cl ratio in glomerular filtrate is about 5 4 Part of the sodium is reabsorbed not in association with chloride but in exchange for potassium and hydrogen ions and this moiety is presumably responsive to the needs of pH homoeostasis rather than to sodium conservation Sodium excretion is increased in osmotic diuresis but not in water diuresis

Potassium

The potassium concentration in glomerular filtrate is only about a thirtieth of that of sodium whereas about half as much potassium as sodium is excreted On a high intake of potassium the excretion of potassium has repeatedly been observed to approach and even in special circumstances to exceed the amount of potassium filtered so that secretion of potassium by the tubules has been established Unequivocal evidence of potassium secretion can be obtained only when the amount secreted exceeds that which is reabsorbed but it is probable that movement of potassium from tubule cell to tubular lumen is taking place even in normal conditions but is masked by a greater movement of potassium in the opposite direction the net process being one of reabsorption This is not merely a terminological matter for Berliner *et al* (1951) have adduced evidence that potassium ions as well as hydrogen ions are available for exchange with sodium ions in the distal tubule The secretion of potassium can be inhibited by mercurial diuretics and by carbonic anhydrase inhibitors Potassium concentration in urine is usually higher than that of plasma but in potassium depletion secretion may be inhibited to the extent of forming a urine of lower potassium concentration than plasma Potassium excretion like that of sodium is increased by osmotic diuresis and unaffected by water diuresis

Urinary Acidity

Pitts (1948 1954) has greatly clarified the mechanisms by which the kidneys can on the one hand eliminate large amounts of anions without depletion of body cation and on the other hand eliminate large amounts of cation in combination with that eminently expendable ion bicarbonate The renal defence against acidosis is based on a cation-exchange mechanism in the distal tubule whereby sodium is reabsorbed and

potassium and hydrogen ions are secreted in exchange in acidosis more hydrogen ions and fewer potassium ions are so exchanged and the total exchange is also increased Not all the hydrogen ions disposed of in this way go out unchanged, some are added to ammonia to form ammonium ion which is then available to combine with anion in the urine without fall in pH Under normal conditions of diet the urine is acid and both the cation exchange mechanism and ammonia formation are active though not to the enhanced degree found in a pathological extrarenal acidosis When the plasma bicarbonate is increased by a metabolic alkalosis excessive *amounts of bicarbonate reach the distal* tubule where they inhibit the Pitts cation *exchange mechanism* so that large amounts of cation are excreted in combination with bicarbonate In a respiratory alkalosis where large amounts of bicarbonate are excreted *in spite of a lowering of plasma bicarbonate there must* clearly be a depression of bicarbonate reabsorption and Pitts has now shown that this is related to the low CO_2 tension in the plasma rather *than to the rise of plasma pH conversely the low bicarbonate excretion* in spite of a high plasma bicarbonate level in respiratory acidosis is related to the high CO tension in plasma

Urea

More urea is filtered at the glomeruli than is ultimately excreted *but it is generally held that reabsorption of urea is a passive diffusion,* and not a regulated process Urea is a highly diffusible substance being present in the same concentration throughout body water, with the *exception of renal tubule fluid in which urea becomes gradually* concentrated at times to a concentration more than a hundredfold that of plasma it is not surprising that some of the urea appears to leak back *during the massive reabsorption of water and other solutes which* accomplishes this concentration process The back diffusion of urea is demonstrably greater at low urine flows than during a diuresis and a *correction for the greater back diffusion of urea at flow rates less than* 2 ml /min is included in Van Slyke s calculation of standard urea clearance At flow rates above 2 ml /min the effect of urine flow on *urea output can be neglected for practical purposes* and the maximal *urea clearance is then used Even the maximal* urea clearance is only about two thirds of the inulin clearance so that about a third of the *filtered urea leaks back even at high urine flows* It is possible that one limiting factor on the power of the kidney to concentrate urea may be the considerable osmotic work performed in doing so the high urine *plasma ratio for urea and the high* rate of urea excretion combine to make the osmotic work done in concentrating urea greater than that involved in excreting all other urinary constituents This aspect of urea *excretion* has been emphasized by Newburgh (1943) but we must

remember that the kidney has a total energy consumption about a hundred times that required for the most efficient performance of the osmotic work required of it In spite of this thermodynamic difficulty the experiments of Addis (1948) show that increase in the amount of urea requiring excretion has an unfavourable effect on the survival of partially nephrectomized rats we can perhaps recall this result for its therapeutic bearings without necessarily accepting osmotic work as the essential factor

Other Substances

At normal plasma levels of *creatinine* the creatinine clearance is of the same order as the inulin clearance and can be used as an index of GFR When creatinine is administered the clearance of creatinine rises indicating tubular secretion Because of this potentiality of tubular excretion and the difficulties of measuring plasma creatinine accurately the creatinine clearance is probably not an exact measurement of GFR but it can be useful in observations extending over periods so long as to preclude infusion of substances such as inulin *Glucose* is almost completely reabsorbed in the proximal tubules at normal plasma levels When the plasma glucose level is raised the reabsorptive capacity of the tubules is exceeded and glucose appears in the urine not in traces as is normal but in amounts detectable by the usual tests The maximum reabsorptive capacity of the tubules for glucose can be measured by raising the blood glucose to levels well above the usual threshold and subtracting the amount of glucose excreted from the amount filtered (i e plasma glucose × GFR) the result is known as the glucose T_m or T_mG This mechanism of controlled excretion by a maximal tubular reabsorptive capacity or T_m is not uncommon and T_m has been determined for *amino acids phosphate uric acid* and other substances Substances secreted by the tubules commonly have a similar quantitative limit and secretory T_ms have been determined for phenol red diodone and *p* aminohippurate by subtracting filtered from excreted amounts When a substance is both secreted and reabsorbed—e g potassium—it is not of course possible to determine the quantitative maxima of tubular performance in respect of that substance

In summary then some substances such as urea and creatinine are excreted in amounts limited only by the plasma level and filtration rate and in the case of urea the ability of the tubules to restrain backward diffusion their excretion can fairly be described as unregulated Other substances such as water sodium and potassium have their excretion determined not only by the amount filtered but also by variations in tubular behaviour usually under hormonal control but sensitive also to other influences such as the carbon-dioxide tension in blood or renal tissue this group includes the quantitatively important

constituents of body fluid and homoeostatic control is normally very efficient For a third group of substances including glucose amino acids and phosphate, excretion goes on at high plasma levels and diminishes very greatly at low plasma levels this being effected by a maximum tubular reabsorptive capacity The description 'organs of excretion applied to the kidneys does scanty justice to their varied resources of excretion homoeostasis and conservation in respect of different substances even the main outlines of renal syndromes can be portrayed only in relation to this versatility of renal performance

Syndromes of Renal Dysfunction

In surveying the effects of renal disease on metabolism we shall do well to avoid any attempt to follow out individual disease processes which would make an account both complicated and repetitive and in the end inadequate Instead of this we shall discuss some half-dozen syndromes of abnormal renal behaviour each of which can be caused by a number of pathological processes In addition to avoiding the debatable ground of the classification of renal diseases this procedure should make for economy of presentation since the main syndromes of renal dysfunction are much less numerous that the morbid anatomical patterns which underlie them The localization of specific activities to different segments of the nephron is still far from complete, and it is perhaps not surprising that a close correlation between anatomical and physiological changes has still to be attained though we must agree with Oliver (1950a) that such is a paramount aim of renal studies Progress is being made in this direction very largely by Oliver s own technique of micro dissection of nephrons in continuity but it has come mainly in acute renal lesions and in chronic nephritis it is often difficult to correlate structural and functional changes Our first three syndromes are commonly but not exclusively caused by nephritis in one of its phases the others are varied or uncertain in origin but have an impact mainly on the tubules without any striking glomerular changes finally we shall notice the effect of serious extrarenal disease on renal function thereby straying but with excuse from our precise terms of reference

Acute Nephritis (Acute Type I Nephritis, Acute Glomerulo-nephritis)

This syndrome is perhaps more clearly defined clinically than pathologically in that the sequence of sore throat followed after an interval by oliguria haematuria oedema and hypertension is very striking whereas the histological appearances of acute glomerulo nephritis may be observed in other conditions most notably bacterial endocarditis but also in non infective conditions such as primary hypertension (Bell 1946) The occurrence of histological glomerulo

nephritis without the characteristic clinical syndrome is a stumbling block in the classification of nephritis but for our present purpose we can neglect these *formes frustes* and describe the morbid physiology of the typical clinical attack

The urine formed in acute nephritis is diminished in volume and rarely there may be complete urinary suppression Haematuria either obvious or microscopic is present with proteinuria and the sediment contains leucocytes and renal epithelial cells generally moulded with coagulated protein into casts The urine is in general concentrated in appearance and with a specific gravity of 1020–1030 to which albuminuria and haematuria make some contribution but lower specific gravities around 1010 have been observed The elimination both of urea and of salt is inadequate but this is usually related to oliguria rather than to any gross defect of concentration in the tubules The urea retention in body fluid is of moderate degree by comparison with chronic renal failure the blood urea exceeding 100 mg /100 ml only in those patients with unusually severe or prolonged oliguria or with an increased rate of protein breakdown The low output of salt and water is matched by a dilution of the blood and plasma (Roscoe 1950) and this is important in the production of oedema and cardiac failure Peters (1953) has argued that the oedema of acute nephritis is chiefly caused by congestive heart failure but the distribution of oedema in its early stages is quite unlike the hypostatic distribution of cardiac oedema No one would deny that the combination of hypertension and raised blood volume imposes a burden on the heart and in fatal cases myocardial damage has been found though usually only when there has been a continuing infective process during the course of the nephritis For the production of a true cardiac oedema however either a forward or a backward failure must be present and in acute nephritis there is no clinical liver enlargement and no prolongation of circulation time while the oedema and venous filling could be attributed to water and salt retention as regards forward failure the vital link of a diminished circulation to the kidneys is missing for the same tests which show a gross diminution of renal blood flow in primary heart disease give results in acute nephritis which fall in or just below the normal range We would put forward the compromise that the primary cause of oedema in acute nephritis is retention of salt and water by the kidneys but that in some cases cardiac insufficiency can assume increasing importance in determining the distribution of oedema fluid Left ventricular failure may then induce fluid accumulation in the lesser circulation with dyspnoea X ray shadowing and even full blown pulmonary oedema Renal and cardiac insufficiency between them do not entirely exhaust the possible mechanisms of oedema in this disease although the concept of a general increase in capillary permeability

has been discredited by the finding of a raised *plasma volume and a low* protein content in oedema fluid, persistence with a low protein diet may sometimes combine with urinary protein loss to induce a true hypoproteinaemia distinct from plasma dilution The convulsive attacks which may complicate acute nephritis have often been attributed to hypertension or to cerebral oedema, but the blood pressure is not so high as in many patients with essential hypertension and cerebral oedema has not been conclusively demonstrated An alternative expla nation may be a lowered osmolarity of body fluids which experiment ally lowers the electro shock threshold the serum sodium in patients with acute nephritis *may be low presumably because of water retention* in excess of salt, and the convulsive seizures can be aborted by hyper tonic saline injections It may not be entirely irrelevant to this brief discussion of oedema in acute nephritis to mention that we have seen a very similar clinical picture including both peripheral oedema and pulmonary engorgement in a patient with water and salt retention during treatment with phenylbutazone

Clearance studies in acute nephritis have usually shown a normal or slightly reduced renal blood flow with a much greater proportional reduction in GFR the ratio of inulin to diodone or PAH clearance being 0 10–0 15 *instead of around 0 2 The observations of* Bradley (1949) are of special interest in that the validity of the PAH clearance as a measure of renal blood flow was checked by estimating the extent to which PAH had been removed from renal vein blood a few of his patients showed an actual increase in renal blood flow above the normal range Agreement on results has not prevented differences in interpretation The results would be consistent either with afferent arteriolar constriction and normal or increased *glomerular permeability* or with a general reduction in glomerular permeability which would preclude analysis of the renal resistance into its afferent and efferent compartments Smith (1951) favours the second view stating that the glomerular lesion is such as to reduce the extensive filtering surface of the normal glomerulus but grossly to increase its permeability at limited points to protein and even blood It is not easy to see why glomerular capillaries should deviate from the usual behaviour of inflamed *capil* laries merely in order to have it both ways at once in this ingenious manner and there is in fact no direct evidence on the point

Management of Acute Nephritis From a metabolic standpoint the main objects of treatment in acute nephritis are to attain minimal urea production, and to avoid loading with salt and water which cannot be adequately excreted Minimal breakdown of protein is secured by a protein free diet and by lowering endogenous protein catabolism by restricting activity controlling persistent infection and giving enough non protein food to limit the breakdown of protein for energy produc

tion as opposed to the natural wear and tear of structural protein Gamble (1947) has shown that a daily intake of 100 g of glucose is almost as effective in sparing protein as a diet which attempts to satisfy full calorie requirements This amount of glucose can be given in sweetened fruit drinks For mild attacks of acute nephritis even this degree of restriction is not necessary and an ordinary low protein diet can be given In severe attacks with urinary suppression the manage ment should be that of acute anuria to be described later A glucose and fruit juice diet is practically salt free in the milder attacks the low protein diet used should also be salt restricted The water intake must also be restricted to less than a litre a day from all sources if ordinary food is being given this means about 600 ml of added beverages These restrictions should be maintained while oliguria persists and gradually relaxed when the urine volume increases as it may do rather quickly in the majority of cases destined to complete recovery About 20 % of patients with acute nephritis fail to make a clear recovery but either die in the acute attack or progress to latent and ultimately chronic nephritis or run a more rapidly progressive course which may include a stage of massive oedema in which hypo proteinaemia plays some part In this last group the severe protein restriction appropriate to the acute oliguric phase must be modified as soon as it becomes apparent that protein loss in the urine is likely to be massive and prolonged three to four weeks may be taken as a somewhat arbitrary term of severe protein restriction in these lingering patients Latent nephritis of course needs no rigorous dietary restric tions although an excessive intake of protein is probably undesirable

Massive Renal Oedema (Type II Nephritis Nephrotic Syndrome)

This syndrome is characterized by generalized oedema heavy proteinuria increase in plasma lipoids and inconstancy of hypertension and urea retention Its nosology is controversial Ellis (1942) regard ing it as a disease *sui generis* characterized by insidious onset and a poor prognosis whereas most American nephrologists look on it as a stage in the evolution of chronic glomerulo nephritis and discount the usual absence of a previous acute attack as being due to anamnestic fallibility This second view does not effect a real simplification however for they are compelled to admit another category known as genuine true lipoid nephrosis to accommodate those patients usually children who after a long and worrying illness may fight their way through to complete recovery Moreover massive oedema of renal origin occurs apart from idiopathic nephritis in amyloidosis diabetic nephropathy renal vein thrombosis and rarely in association with secondary syphilis

The urine volume is low except during natural or induced remissions

and its sodium and chloride content is very low Urea clearance varies from patient to patient often remaining normal for many months but in other patients showing a rapid falling off with a mounting blood urea in children urea clearances greater than the normal average have sometimes been reported but this is unusual in adults A heavy albuminuria is found 5–20 g /litre amounts in excess of what is usually observed in acute nephritis Casts may contain doubly refracting lipoid material Microscopic haematuria is inconstant and visible haematuria is practically unknown The specific gravity remains normal until the onset of renal failure the massive albuminuria no doubt offsetting the low electrolyte content of the urine

The oedema is generalized involving the serous cavities as well as the face limbs and subcutaneous tissues generally In the absence of hypertension there is surprisingly little dyspnoea to suggest pulmonary collection of fluid Massive protein loss in the urine leads to low plasma protein levels and this must contribute to the oedema, but salt and water retention by the kidneys is also necessary This may indeed represent a response to leakage of saline fluid from the blood stream or it may be conditioned more directly by the kidney lesion A considerable water and salt diuresis with recession of oedema can occur without change in the plasma protein level so that hypoproteinaemia does not in itself furnish a complete explanation of the fluid retention Equally the oedema cannot be due to a pure water and salt retention with dilution of plasma protein for the hypo proteinaemia is too great to be a dilution effect and there is no evidence of dilution of red cells Hypoproteinaemia is certainly an important cause of transit of fluid from the blood stream to tissue spaces and the renal retention of salt and water is in some degree secondary to this but does at times show variations quite independent of plasma protein levels A further difficulty is that the serum sodium level may be moderately reduced in this syndrome as in other states of chronic oedema where more emphasis is currently placed on sodium than on water The complex pathogenesis of the oedema can be further illus trated by reference to the infusion of salt poor human albumin which can induce temporary improvement in the plasma protein level some patients show very little response to this but in others a sodium diuresis is induced and these have a more sustained loss of fluid Moreover in this baffling syndrome a spontaneous remission can effect within a week a recession of oedema which has evaded a succession of salt-depleting expedients deployed over the course of months Apart from genuine improvement the advance of renal failure with polyuria and dimi nished proteinuria from loss of nephrons can less happily diminish the oedema

The pathogenesis of the oedema does not exhaust the uncertainties of

this syndrome Proteinuria has been attributed both to abnormal glomerular permeability and to failure of protein reabsorption by the tubules The observations of Chinard *et al* (1954) and of Hardwicke and Squire (1955) comparing creatinine and protein excretion indicate an abnormal glomerular permeability to albumin and other protein fractions but they do not exclude alteration in tubular protein re absorption as an additional factor The remissions which can be induced by cortisone or corticotrophin in a high proportion of patients with the nephrotic syndrome are of great therapeutic interest but they also raise further problems of pathogenesis Sometimes the effect is limited to a salt and water diuresis which may not appear until a short course of treatment has ended at other times proteinuria is sensibly diminished while in yet other patients prolonged and complete re mission of proteinuria may follow treatment These variable responses could be based on inhibition of aldosterone production on a direct action on glomerular permeability or on suppression of a general allergic reaction Striking water and salt diureses have been observed with prednisolone (Arneil 1956) which is not considered to have any direct action on sodium and potassium excretion A diminished filtra tion of albumin indicated by a fall in albumin inulin clearance ratio has been described by Lauson *et al* (1954) Finally a depression in the α_2 globulin fraction of plasma protein has been observed by Smart (personal communication) in patients whose plasma albumin was rising during effective corticotrophin therapy

The lipaemia has been explained only teleologically as an osmotic compensation for hypoproteinaemia its mechanism is unknown The nephrotic crises have been ascribed to fall in plasma amino acids and treated by amino acid infusions (Emerson and Van Slyke 1942) but usually the clinical picture is one of infection with leucocytosis and the response to penicillin is excellent so that they are hardly now to be reckoned with as a cause of death After this catalogue of unsolved problems it may seem rash to discuss the management of massive renal oedema but we have at our disposal many methods of reducing oedema and all too often the disease runs a course in which patient and doctor have to run the gamut of these snatching symptomatic relief in default of any proved and certain cure At the onset of type II nephritis if there is no sign of rapid progression it is probably best to confine interference to resting the patient in bed and giving a diet low in salt but high in protein about 150 g of protein per diem at this stage spontaneous remissions are not uncommon and it is perhaps wise in this protracted disorder to withhold special and disturbing treatments until they are really necessary The protein content of the diet should be subject to revision on the basis of regular estimations of the blood urea with elevation of this the protein content of the diet has to be

reduced to around 50 g /day When the oedema obstinately increases in spite of dietary treatment as it does all too often, the time has come to consider more active treatment in which we attempt to raise the colloid osmotic pressure of the plasma or to induce a sizeable negative balance of salt and water Salt poor human albumin has been extensively tried in America, and has been known to *relieve oedema significantly* but the amounts required for continued treatment would represent the contribution of several blood donors each day which seems unjustified in treatment which is no more than symptomatic A more attractive treatment economically at least, of the same type is the use of high molecular weight carbohydrates or polyvinyl pyrollidones which act as plasma expanders and also to some extent as osmotic diuretics the solutions used should be dialysed to remove electrolytes and such solutions can be obtained commercially e g salt free Dextran Reticulo endothelial damage has not been reported with these substances as it has with gum acacia Intravenous infusion of 500 ml of a 6% solution *of the polymer often produces a satisfactory diuresis and this* can be repeated at three day intervals Treatments directed mainly at the salt balance include exchange resins by mouth and mercurial diuretics Cation exchange resins in the potassium and ammonium cycle can be given in doses up to 100 g /day, but it is not easy for patients to persevere for long periods as is often necessary with more than 50 g /day this treatment is essentially a means of ensuring a really low intake of sodium such as is required to get below the very low urinary sodium output in these patients A trial of mercurial diuretics to raise the urinary sodium and chloride loss directly is worth making but the response in terms of diuresis is often poor, in which case mercurials should be *discontinued Finally mechanical removal of fluid* by paracentesis and by the insertion of modified Southey s tubes into the legs in which oedema fluid has been encouraged to accumulate by postural drainage may be more dramatically effective than any other measure (Platt 1952a)

Chronic Renal Failure (Uraemia)

This syndrome represents the end results of any one of a great variety of progressive nephropathies *Terminal nephritis* chronic pyelonephritis chronic obstruction to urinary outflow and the malignant phase of essential hypertension are among the commonest but to these we can add polycystic kidney congenital hypoplastic kidney renal tuberculosis radiation nephritis renal lesions complicating bacterial endocarditis and collagen diseases and the renal excretory failure which often supervenes on various syndromes of the Fanconi *group to be discussed in a later section* We shall be concerned here only with the metabolic upset in chronic renal failure but clinically

the picture may be dominated by the secondary hypertension which commonly but by no means invariably accompanies progressive renal disease

Examination of the kidneys discloses a great loss of functioning nephrons whose glomeruli are obliterated by hyalinization and their tubules atrophied alongside may be observed hypertrophied tubules and there is a general distortion of renal architecture which has led Oliver (1950b) to question whether concepts applicable to the normal kidney with a relatively homogeneous population of nephrons can retain their validity in relation to the individualized nephrons found in renal failure At the present time this is something of a phantom problem in that we have not the techniques to define the performance of separate human nephrons and Platt (1952b) has shown that a useful analysis can be made of function in the failing kidney on the assumption that simple loss of nephrons represents the most important change in renal structure It is quite clear that the renal tubule in failure handles the solute load presented to it differently from the tubule in normal kidneys but Platt has suggested that the abnormality of the response may be due not to inherent defects in the tubules themselves but to the abnormal conditions imposed by the need for a small number of surviving nephrons to support the whole excretory load The detailed evidence for this interpretation of some of the phenomena of renal failure in terms of osmotic diuresis may be found in the original paper

The urine flow is high in chronic renal failure except in the last few days of life when there may be oliguria or even anuria The normal diurnal rhythm of urine flow is lost and the consequent nocturia is a troublesome symptom whose presence may be clinically suggestive of renal failure There is a diminished ability to respond by changes in the specific gravity of the urine to water loading or restriction and a state of isosthenuria may be reached in which the specific gravity of the urine is fixed around 1010 corresponding to a protein free filtrate of plasma in this respect although considerable differentiation of glomerular filtrate persists to the end notably a reabsorption of salt and water and some concentration of urea The proteinuria is not heavy in comparison with the earlier stages of nephritis but the boiling test practically always shows a trace of albumin the lowered concentration of urinary protein in the terminal stages can be related to the polyuria and to there being a smaller number of nephrons as sources of protein The urea clearance is depressed and the blood urea concomitantly raised Inulin and diodone or PAH clearances must obviously be interpreted with great reserve but they are all depressed and renal vein blood may contain PAH in amounts greater than 10% of the systemic concentration Earle Taggart and Shannon (1944) found an increase in the ratio of diodone clearance to diodone T_m which

could be interpreted as indicating hyperaemia of surviving renal tissue in chronic nephritis Raaschou (1948) in patients with chronic pyelonephritis found a low C_D/T_{mD} ratio suggesting relative ischaemia of renal tissue in this disease Smith (1951) suggests that the discrepancy may be related to the constraint on renal blood flow imposed in pyelonephritis by a degree of capsular scarring and constriction greater than is found in ordinary nephritis

In spite of a persistently and considerably raised blood urea these patients may be able to lead a surprisingly normal life especially in the absence of hypertension Given a fixed clearance the rise in blood urea level will increase the amount of urea eliminated each day and if this then falls within the range of urea production an equilibrium state may be maintained in which the blood urea is indeed raised but further retention of urea is kept in abeyance Sodium balance may also be maintained in spite of a great diminution in the filtered load of sodium through loss of glomeruli this can be done only if each surviving tubule rejects a considerably greater than normal proportion of the sodium presented to it and comparison of sodium and inulin or creatinine clearances shows that this is in fact what happens Normally about 1% of filtered sodium is excreted whereas in renal failure this may increase to 5% or more A few patients usually suffering from chronic pyelonephritis have been observed to excrete so much salt as to become dehydrated these patients with salt losing nephritis may simulate Addison s disease superficially but they do not respond to DCA nor do they show the signs of glucocorticoid deficiency a number have however, been pigmented For the most part however patients in renal failure look after their sodium balance very well unless they have extrarenal dehydration from vomiting or diarrhoea Although individual patients in renal failure have been observed to have symptoms associated with hyperkalaemia and in other cases with hypokalaemia the plasma potassium level does not usually deviate far enough from the normal to be responsible for any symptoms In advanced renal failure the amount of potassium filtered falls well below the dietary intake and retention of potassium within the body can be prevented only by secretion of potassium by the renal tubules again comparison of potassium clearance with inulin clearance confirms the preponderant tubular secretion of potassium which is necessary to explain the observed facts of potassium balance Water balance is also well maintained although an increased intake of water is needed to sustain the polyuria patients have been observed however in whom the need for water goes beyond this in that they are in a state of continuous water diuresis Their state resembles diabetes insipidus with a urinary specific gravity of 1001 or 1002 but they do not respond to injections of ADH These cases of water losing nephritis (Oleesky

and Roussak 1954) and those of salt losing nephritis are however rare exceptions and the homoeostasis of the amount and osmotic tonicity of body fluid is usually well maintained until the final stage of rapid deterioration of all renal functions is reached

There are however important changes in the composition of body fluid apart from the striking urea retention Urea itself is not a particularly toxic substance as is witnessed by the tolerance of animals to large doses of urea and perhaps most clearly by the elasmobranch fishes which defend their body fluid against the osmotic attraction of sea water by maintaining a blood urea of 2000 mg /100 ml Nevertheless when a patient comatose in uraemia has his blood dialysed in the artificial kidney he regains consciousness suggesting that substances more toxic than urea have been removed as well as the urea which affords a measure of the extent of effective dialysis It must be confessed however that search for a single toxic substance or group of substances which could account for uraemic coma has not been successful and that older theories based on phenols guanidine and other retained substances have not been confirmed We have seen that the balance of the main structural elements of body fluid sodium potassium and water is not often greatly disturbed but alteration in plasma pH and in calcium and phosphate can account for some of the symptoms of uraemia while others are due to the associated hypertension inflicting cerebral damage I can only express the personal opinion that in uraemic coma some significant factor has so far escaped detection and analysis of the dialysate from uraemic patients who recover consciousness may ultimately yield a tediously won reward In the meantime we must mention the electrolyte abnormalities which are known to play some part in the pathogenesis of the uraemic state

The renal defence against acidosis is considerably impaired in chronic renal failure Not only does loss of glomeruli interfere with the elimination of fixed ions such as phosphate and sulphate but the base sparing effected by urine acidification and the formation of ammonia is greatly diminished Under normal conditions of metabolism the kidney is required to excrete about 50 m equiv /day each of phosphate sulphate and organic acid In renal failure the amount of each of these substances in the plasma is increased and the plasma bicarbonate is reduced being kept so by increased elimination of carbon dioxide by the lungs The increase in plasma phosphate is perhaps of special importance in that it is associated with a low level of plasma calcium the underlying mechanism probably being depression of calcium absorption by the raised phosphate content of alimentary secretions which promotes the formation of relatively insoluble calcium phosphate in the bowel Other factors of importance in renal rickets are parathyroid hyperplasia which causes osteitis fibrosa and acquired

vitamin D resistance which contributes to the low plasma calcium levels and the osteomalacia These matters are more fully discussed in the chapter on metabolic bone disease here we need only say that in chronic renal failure varying degrees of osteomalacia osteitis fibrosa and even osteosclerosis are not uncommon and may be the cause of bone pains and deformity (Stanbury 1957)

It will have been apparent even from this summary account that adaptive processes may mitigate the progress of renal failure and in our present ignorance it is possible to do more harm than good by meddlesome attempts at treatment As an example of this administration of alkalis such as sodium lactate may relieve dyspnoea but it may on the other hand induce tetany by depressing the fraction of plasma calcium which is ionized and a high sodium intake is in any case risky in patients who are often threatened with hypertensive cardiac failure Elaborate dietary measures are not indicated in a disease whose end is certain and in which mere prolongation of life may be a disservice to the patient and his relatives but a low protein diet will *extend the relatively symptomless phase of the disease* not only by diminishing urea production but also by lowering the effective intake of fixed acid The salt and fluid intake should be liberal except when hypertensive heart failure dominates the clinical picture in the rare salt losing nephritis extra salt should be given There is no evidence to justify interference with the patient s habits of smoking and drinking so long as they are supported by his inclinations

Acute Renal Failure (Acute Anuria, Renal Tubular Necrosis)

In acute renal failure, the production of urine either ceases altogether or more commonly falls to a few ounces per day an amount grossly inadequate alike for excretion and homoeostasis The syndrome may be produced by many differing morbid processes including surgical *and obstetrical shock calculous obstruction* intravascular haemolysis severe sodium depletion bacterial toxaemia poisoning with mercury carbon tetrachloride oxalate and many other substances acute nephritis or pyelonephritis and myeloma and sulphonamide kidney in which tubular blockage may play some part A very small proportion *of cases of acute renal failure are* caused by primary renal or urinary tract disease For the most part the kidney is damaged by primary extrarenal disease our understanding of the pathogenesis and natural history of this type of renal damage has been greatly augmented by the recent studies of Bull *et al* (1950) and Oliver *et al* (1951) Examination of the kidneys by ordinary tissue sections had indicated the importance of damage to the renal tubules and had shown occasional rupture of tubules into veins but had largely failed to define the nature *and situation of the tubular* lesions Oliver s technique of micro-dissec

tion of the nephrons in continuity has exposed one cause of the very considerable confusion which prevailed in that his team were able in a large series of kidneys to demonstrate two quite distinct tubular lesions each of them capable of producing anuria Kidneys from patients with renal injury from specific poisons such as mercuric chloride and sulphonamides showed mainly a necrosis of the parenchymal cells of the proximal tubules the surrounding basement membrane retaining its continuity On the other hand kidneys from patients with shock or intravascular haemolysis showed a graver tubular involvement in that any segment of the tubule might be damaged and the damage was more complete with dissolution of the basement membrane and consequent rupture of the tubule into surrounding tissue and even veins this lesion is described as tubulorhexis The separation of the two groups was not absolute in that severe toxic damage to the kidney might be complicated by tubulorhexis but the ischaemic kidneys did not show the rather generalized proximal necrosis with intact basement membrane which was characteristic of the toxic group A further important contribution by Oliver *et al* (1951) was the experimental production of tubulorhexis by renal ischaemia which consolidated the inference from the clinical material that ischaemia was responsible for this type of lesion In neither type of renal damage was there any extensive blocking of tubules as dissected in continuity but material from the myeloma kidney was not included in the series The functional studies of Bull Joekes and Lowe (1950) not only confirm the presence of gross renal ischaemia in acute anuria but also extend our information to those patients who ultimately recover and define the stages of recovery There was gross impairment in renal blood flow and glomerular filtration rate and in the extraction of *p* aminohippurate from the blood which did perfuse the injured kidneys From a functional standpoint the renal performance could be divided into a phase of onset an anuric or oliguric phase and early and late diuretic phases Evidence of faulty tubular function was outstanding in the anuric and early diuretic phases but in the late diuretic phase there were signs of recovering tubular function In the early diuretic phase large amounts of electrolytes were lost in the urine and depletion of sodium and potassium has been observed Glycosuria is unusual in renal tubular necrosis although Bull found low values for T_mG this was at a time when the GFR was notably reduced so that the reabsorption of glucose in surviving nephrons might still be normal as is suggested by the histological appearance of the relevant segment of proximal tubule These two studies have had an important influence on the management of anuria since they show that recovery can come only from improvement in tubular function which cannot be achieved either by loading the body with fluid or by giving diuretics The toxic necrosis of proximal

tubules is susceptible of complete repair the tubules actually ruptured in ischaemic kidneys are unlikely to be repaired but this type of damage is patchy and enough nephrons escape damage to maintain adequate renal function once the acute reaction to necrosis of the damaged tubules has settled down There are however a minority of patients in whom the ischaemic damage produces a massive rather than a patchy cortical necrosis, and this type of lesion is almost certainly irrecoverable but the existence of this group of patients cannot influence management as they are detected only after death although failure of recovery of urine flow within two weeks especially after obstetric haemorrhage, can raise the suspicion of massive cortical necrosis Treatment is in fact based on the hypothesis that the renal lesion is usually capable of complete or partial recovery and the emphasis has shifted from attempts to force a diuresis to a conservative regime designed to maintain life until the kidneys recover

In the anuric phase the body has no means of eliminating an excess of water electrolytes or urea apart from the considerable loss of water by skin and lungs and the small electrolyte loss in sweat and faeces There is a steady increase in blood urea, about 30 mg /100 ml daily in uncomplicated cases on a high-calorie low protein diet but the blood urea often climbs much more steeply through an increased rate of protein breakdown When no precautions are taken fluid quickly collects in the body, and obvious oedema appears on a conservative regime water retention exceeds that of salt and the plasma sodium level is commonly reduced to about 120 m equiv /L Hamburger and Mathe (1953) have pointed out that breakdown of body fat makes available large amounts of water so that an allowance of a litre per day of water by mouth is probably too high they have shown shrinkage in the extracellular fluid with loss of water into the cells predisposing to water intoxication Another explanation of the low plasma sodium may be transfer of sodium into the cells as the mechanism which normally maintains a low concentration of intracellular sodium becomes impaired There is usually an increase in the plasma potassium in patients with anuria even on a diet free from potassium the source of extracellular potassium being the breakdown of tissue protein and consequent discharge of intracellular fluid A considerable metabolic acidosis is also present with hyperpnoea and a lowered plasma bicarbonate Plasma inorganic phosphate is increased, and calcium diminished

Conservative management of patients with anuria is based on a diet adequate in calories restricted in water content and free from protein and electrolytes The practical problems involved have been effectively tackled by Bull *et al* (1949) who use a fluid diet given by plastic stomach tube as a slow drip, containing each day,   of arachis oil and

400 g of glucose made up to a litre with distilled water and emulsified with gum acacia Vomitus is strained and covertly added to the diet The widespread use of this regime has undoubtedly averted deaths from heart failure and pulmonary oedema the commonest causes of trouble in the first week of anuria It is possible that even this restricted amount of fluid is too great and we should be content with a lower calorie intake in 500 ml of water Another important factor in the later mortality from anuria is increase in plasma potassium to toxic levels predisposing to cardiac failure or sudden cardiac arrest The conservative regime alone does not control the plasma potassium level adequately especially when protein breakdown is increased As an emergency measure insulin and glucose will lower the plasma potassium but a long term effect can be obtained by a cation exchange resin in the sodium cycle given by mouth or enema in amounts up to 100 g daily When vomiting or intolerance prevent oral feeding Bull (1952) recommends the infusion of 20–50% glucose solution by plastic catheter passed through an arm vein into the superior vena cava by which means a calorie intake of over 1000/day can be maintained and some control of plasma potassium exerted Anaemia should be corrected when present and infection controlled by antibiotics The low plasma sodium level and acidosis seem to challenge treatment but large saline infusions are clearly undesirable because of the risk of heart failure Hamburger and Mathe advocate giving sodium in order to withdraw water from the cells I have used molar sodium lactate in amounts of 80–200 ml and correction of the biochemical abnormality can certainly be attained in this way but clinical improvement is difficult to judge in this condition where spontaneous remission can occur When diuresis first becomes established homoeostatic regulation of water and electrolytes is still very imperfect and dehydration may appear unless the restrictions on fluid and electrolyte intake are relaxed The change in management should however be cautious in that there is usually an excess of water and electrolyte within the body when diuresis begins In spite of considerable advances in knowledge and therapeutic methods a patient with anuria still represents a problem demanding close attention to detail even under conservative management when diuresis is delayed dialysis may have to be considered but this demands close biochemical control if an artificial kidney is not available the best method is intermittent peritoneal dialysis described in detail by Grollman (1954) The conservative régime is indicated in almost all patients with anuria the exceptions being patients with urinary obstruction requiring urological treatment and those in whom the renal lesion is based on severe sodium depletion To cause anuria sodium depletion must be really severe and there will be a history of loss of saline fluid and very obvious clinical dehydration in contrast to the

rather overhydrated tissues seen in other types of anuria these patients must of course be treated by vigorous sodium replacement Splanchn or spinal block and renal decapsulation, have not been shown to influence the renal lesion and should not be practised on present evidence A well documented account of acute renal failure based on very extensive clinical experience, is available by Merrill (1955)

Renal Tubular Syndromes

In this section we consider a group of renal disorders in which the main abnormality lies in the tubules the various anomalies of function being to begin with at least highly specific though there is a tendency later for glomerular filtration to be seriously impaired and the end result is commonly renal failure These syndromes are of considerable interest and importance to the general physician and surgeon because of their mode of presentation instances have been recorded in which patients with these disorders have been treated for diabetes, rickets or hepatic disease for some time before the renal abnormality was detected Many of the syndromes are familial in incidence and incomplete syndromes in siblings of patients with the full syndrome are not uncommon Many of the syndromes were first found in childhood although adult analogues are now being encountered In most cases the cause of the syndrome is unknown and also the localization and nature of the tubular defect a partial exception is the classical Fanconi syndrome in which there is an absence of phosphatase in the proximal tubule (Stowers and Dent, 1947) and also a peculiar swan neck narrowing of the stretch of proximal tubule nearest the glomerulus (Clay Darmady and Hawkins, 1953) Our ignorance of aetiology and mechanism and the considerable variation in expression of these syndromes makes their classification a somewhat arbitrary affair (Jackson and Linder 1953) For our present purpose it will be enough to mention the main defects which have been observed in tubular function with a brief statement on clinical aspects An excellent review of tubular syndromes causing bone disease with particular emphasis on the genetic aspects of these syndromes is now available by Dent and Harris (1956)

Renal Amino Aciduria This is found in the Fanconi syndrome in hepato lenticular degeneration (Wilson s disease) and in idiopathic cystinuria It has to be distinguished from the amino aciduria secondary to an accumulation of amino acids within the body such as is found in primary hepatic failure and in cystinosis a normal or low plasma level of amino acids is the essential mark of a renal amino aciduria

In the Fanconi syndrome amino aciduria is usually accompanied by glycosuria and phosphaturia and there may also be systemic acidosis hypokalaemia defective acidification of the urine with or without

adequate ammonia formation and varying degrees of albuminuria isosthenuria and chronic renal failure Clinically the most constant symptom is bone pain caused by osteomalacia resistant to vitamin D and often producing pseudo fractures (Looser s nodes) The conjunction of glycosuria and ketonuria (due to a resorptive defect in respect of keto acids) may create confusion with diabetes (Milne Stanbury and Thomson 1952) Hepatic cirrhosis and renal excretory failure are common in long standing cases Bone pain usually responds to high doses of calcium and vitamin D and an alkalinizing mixture benefit has also been claimed from methyl testosterone (Anderson Miller and Kenny 1952)

Most of the manifestations of the Fanconi syndrome can be interpreted in terms of a primary renal disorder but in hepato lenticular degeneration the abnormal excretion of amino acids does not account for the hepatic cirrhosis and neurological manifestations and there is some evidence that an abnormality of copper metabolism may underlie the whole syndrome (Denny Brown and Porter 1951) Although both have a familial incidence the Fanconi syndrome and Wilson s disease are clearly separated by the skeletal lesions of the one and the abnormalities of the basal ganglia in the other (Matthews Milne and Bell 1952) Moreover the amino aciduria of Wilson s disease is associated with a high excretion of copper and glycosuria and phosphaturia are not present Some cases of Wilson s disease have improved clinically when copper was mobilized from the tissues by BAL or penicillamine In idiopathic cystinuria the amino aciduria is less general than in the other renal syndromes but it is not limited to cystine itself there being also an increased excretion of lysine and arginine apart from a liability to the formation of cystine calculi patients with this syndrome enjoy good health (Dent and Rose 1951)

Renal Tubular Acidosis Leaving aside the defect in urine acidification associated with general renal failure a specific defect of urine acidification has been observed both in infants and in adults leading to a hyperchloraemic acidosis with an increased excretion of base including calcium which may then be deposited in the distal tubules to produce one type of nephrocalcinosis (Greenspan 1949) Conversely prolonged elevation of the plasma calcium in hyperparathyroidism Paget s disease with immobilization vitamin D intoxication or even a prolonged high intake of milk and alkalis can lead to deposition of calcium in the kidneys and consequent defective acidification of the urine The hyperchloraemic acidosis which may follow uretero sigmoidostomy is largely related to chloride absorption from the bowel but there is often an associated pyelonephritis with defective urine acidification There is some doubt as to the mechanism of the idiopathic renal tubular acidosis The essential feature of the syndrome is a urine which is more

alkaline and contains less ammonia than would be appropriate to the degree of systemic acidosis present at the time this abnormality can be clearly displayed by collecting urine after a 3 g dose of ammonium chloride Normally the urine pH falls to 5 or less and the ammonia excretion rises both these responses are impaired in renal tubular acidosis and the urine may even remain alkaline Latner and Burnard (1950) have suggested that there is a failure of bicarbonate absorption and an increase of chloride absorption in the proximal tubule Their evidence for this rests to some extent on their observation that the partial pressure of carbon dioxide in the urine was consistently higher than the pCO_2 of plasma an observation which they interpret as meaning an intact acidification mechanism in the distal tubule Kennedy *et al* (1952) have since shown that high urine pCO_2 is produced by mixing of urine of differing bicarbonate and buffer content from different nephrons so that the localization of impaired function is still uncertain There is no doubt however as to the finding of an increased bicarbonate and diminished chloride excretion, and the inverse changes in the plasma concentration of bicarbonate and chloride

The clinical picture of renal tubular acidosis is, in infants predominantly one of acidosis with hyperpnoea and polyuria leading to dehydration later bone defects may appear and calcification of the kidneys be demonstrated radiologically The immediate treatment is by administration of sodium bicarbonate in amounts sufficient to control the acidosis in those cases which appear in infancy usually about the age of six months the tendency to acidosis may disappear after one to two years treatment, but recovery is not necessarily complete as nephrocalcinosis may later become radiologically apparent In adult patients acidosis and dehydration are less prominent and the condition usually presents as bone pain or may remain clinically silent until complicated by renal excretory failure In treatment it is important to decide whether the renal acidosis is primary with secondary nephrocalcinosis or whether the primary change is one of disordered calcium metabolism with secondary renal damage With primary renal disease the plasma calcium is in or below the normal range while in hyperparathyroidism or calciferol intoxication the plasma calcium is usually raised The acidosis can be controlled by Shohl s sodium citrate—citric acid mixture, but when a raised plasma calcium is present, hyperparathyroidism Paget s disease sarcoidosis and calciferol overdosage must be sought for and if possible corrected Acute calcium toxicity may require de ionization of calcium by infusion of sodium citrate or one of the newer calcium complexing substances such as Versene

Renal Glycosuria This has already been mentioned as occurring in the Fanconi syndrome but it is more commonly met with apart from

amino aciduria as a condition of no great clinical import in itself but requiring differentiation from diabetes mellitus and from other metabolic causes of excessive excretion of reducing substances such as pentosuria The essential feature of renal glycosuria is the presence of glucose in the urine in substantial amounts at levels of plasma glucose well below the mean renal threshold of 180 mg /100 ml The mechanism of renal glycosuria has been reviewed by Govaerts (1952) In some patients the maximal reabsorptive capacity for glucose (T_mG) is unusually low but in other patients the T_mG at high plasma levels of glucose may be within the normal range This latter condition may be due to excessive filtration in a proportion of nephrons whose private T_mG is then saturated at quite low plasma levels or by passive diffusion of glucose into the distal nephron (Robertson and Gray 1953) An isolated renal glycosuria may persist for many years without the appearance either of other renal dysfunction or of diabetes mellitus In diabetes mellitus itself the T_mG is often increased giving a high threshold but in some patients the threshold of appearance of glucose may be lower than normal a combination of renal and metabolic diabetes

Functional Renal Failure (Extrarenal Uraemia)

We have already noted that the kidney can be seriously damaged by disease originating in other organs for example acute renal failure with tubular necrosis nephrocalcinosis and renal failure in malignant hypertension In this section we are concerned with those changes in renal performance which are produced by extrarenal disease without the kidney itself sustaining any clear cut structural damage either temporary or progressive The common factor in all these states is probably a reduction in blood supply to the kidney sufficient to affect its function but not to cause necrosis of its substance but in addition to this the behaviour of the tubules in respect of salt and water may be modified by changes in their hormonal control as is most clearly seen in Addison s disease but may also be concerned in the production of cardiac oedema We shall not however discuss here the part played by the kidney in the production of generalized oedema which has been noticed in the chapter on water and electrolytes nor the changes in renal function in Addison s disease Leaving aside these instances of homoeostatic renal dysfunction from extrarenal causes we are left with renal excretory failure which has now been described in many different non renal diseases

The amount of urea in the body represents a balance between production of urea in protein breakdown and elimination of urea by the kidney Elimination of urea by the skin and bowel does indeed reduce the amount of urea in the body but it cannot by itself lower the con

centration of urea in body fluids as these channels of excretion do not produce a concentrated solution of urea such as urine, this explains the dangerously large amounts of fluid which have to be used in any type of dialysis designed to lower the blood urea Most types of extrarenal uraemia owe something to increased protein breakdown as well as to impaired renal function and are to that extent truly extrarenal, but the increase in blood urea which can be produced by protein break down, or even by urea ingestion is modest and impairment of renal function has usually been demonstrated in these instances of extrarenal uraemia where it has been sought The balance between excessive production of urea and impaired renal excretion is no doubt variable and its determination somewhat academic once the existence of both components has been recognized

Extrarenal uraemia of varying degree has been observed in severe dehydration after massive haemorrhage, and also in acute fever and in cardiac and hepatic failure We need not recapitulate here the clinical causes of severe dehydration Massive haemorrhage is more likely to cause a significant uraemia when the blood is retained for a time within the body, as in bleeding from peptic ulceration In acute fevers and in cardiac failure the rise in blood urea is moderate When the blood volume is reduced either by direct blood loss or by loss of plasma volume in sodium depletion the blood flow through the kidneys is diminished The same thing happens when cardiac output is reduced, even in the presence of a normal blood volume and in hypovolaemic states generally the renal circulation is reduced to an even greater extent than the cardiac output This is a reasonable adaptation to acute fall in blood volume or cardiac output as normally the kidney gets about a quarter of the cardiac output which is necessary for proper urine formation but greatly in excess of the kidney s metabolic requirement, in states of emergency, urine formation is properly sacrificed to the maintenance of an adequate carotid blood flow Short periods of ischaemia seem to produce little structural damage to the kidney but they have to be paid for in a uraemia which is often symptomless longer periods of ischaemia produce organic changes in the kidney as we have already discussed The practical corollary to this in the management of haemorrhage and shock is obvious

Although a renal functional impairment which falls short of acute tubular necrosis is usually of little direct importance in comparison with the primary disease underlying it its detection may still be of value as an indication that blood or fluid replacement has not been adequate The raised blood urea of functional renal failure can usually be distinguished from chronic renal disease by the detection of a recognized cause of extrarenal uraemia and by the oliguria which accompanies it In chronic renal failure polyuria is characteristic and the

only type of functional renal failure likely to be confused with chronic renal failure is alkalosis from alkali ingestion in which the urine volume may remain fairly high an alkali reserve estimation will make the distinction clear, if there is any doubt clinically e g because of inability to give a proper history The distinction between extrarenal uraemia and acute renal failure with tubular necrosis may be difficult This is to be expected as the two states probably both represent a response to renal ischaemia and differ only in the degree or duration of the renal insult so we cannot expect much help from knowing the circumstances of onset Evidence of haematuria of intravascular haemolysis and very severe oliguria or anuria make it likely that the kidney is structurally damaged The distinction is not academic for on it may depend the decision whether to restrict fluids or to give fluids freely by way of sodium replacement When there is doubt it is probably safest to restrict fluids until clear evidence of oligaemia can be obtained from the haematocrit or plasma sodium estimation Extrarenal uraemia in itself needs no specific treatment but demands correction of the state of hypovolaemia or dehydration which has induced it

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CHAPTER 4

THE METABOLIC DISTURBANCES FOLLOWING INJURY

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THE infliction of an injury of any type immediately sets in motion a train of events associated with the maintenance of the stability of the organism *during the period of stress the repair of the damaged tissues and the* eventual restoration of the body to normal composition and activity The investigation of these complex processes is far from complete and *their interpretation* is difficult and at present largely tentative *It is* however, becoming clear that the metabolic response is influenced chiefly by the nature and severity of the inflicted injury and by the condition of the patient (Cuthbertson 1942 1945 1954 Howard 1945 Moore and Ball 1952) The features are most easily studied in a young adult who receives a surgical operation for a condition which has not impaired his nutritional state or general health The importance of understanding this physiological response to a major wound of soft tissues needs no elaboration it forms a guide to general medical and surgical care and a basis for the definition and study of the abnormal An account of the metabolic changes commonly observed in a healthy adult after exposure to trauma is accordingly provided in some detail Thereafter modifications of this response will be described and the mechanism of the changes and therapeutic considerations will be discussed

The Approach to the Study of Metabolism after Trauma

A *knowledge of the body composition* both of healthy adults and of patients with diseases that interfere with nutrition is the first requirement in the study of the metabolic disturbances for it is on this background *that the later changes will be superimposed* Furthermore the original condition of the patient influences considerably his subsequent response to an injury

The body *composition of living human subjects* has been most fruitfully studied by isotope dilution techniques (Moore, 1946 1954 Corsa Olney, Steenburg, Ball and Moore 1950, Schloerb Friis Hansen Edelman Soloman and *Moore 1950 Forbes and* Perley 1951 Edelman, Haley Schloerb Sheldon Friis Hansen Stoll and Moore 1952a, Miller and Wilson 1953 Moore McMurrey Parker and

Magnus 1956) though various other methods have from time to time been attempted (McCance and Widdowson 1951 Keys and Brozek 1953) The principle of all these methods has been fully described by Moore and his associates (Edelman Olney James Brooks and Moore 1952b) A known amount of the isotope is added to the body and the quantity excreted during the establishment of equilibrium of distribution is measured The dilution of the isotope in the corresponding natural element in the body is measured and the total amount of the element with which the isotope has exchanged is calculated There are many limitations to these measurements The establishment and measurement of dilution equilibrium in an essentially dynamic system may be a matter of some difficulty in proof and practice The total exchangeable mass of the element is not necessarily the total amount in the body For example sodium isotopes do not measure a large fraction of the sodium in bone (Davies Kornberg and Wilson 1952a and b Edelman James Baden and Moore 1954 Miller Munro Renschler and Wilson 1954) In the case of measurements of total body water with deuterium oxide the deuterium exchanges rapidly with the hydrogen of water but also to a slight extent is incorporated in organic molecules during the two to three hours required for the measurement in healthy subjects These and other problems have been fully discussed in the relevant publications cited above but in spite of the difficulties there can be little doubt that these estimates offer the most reliable picture of body composition at present available Already measurements have been made of the body composition of healthy adults with respect to water sodium potassium and chloride Unfortunately there is a wide range in normal values even when these are expressed on a body weight basis This is largely due to the great variations in fat content of the body In the male water represents about 60% of the body weight and in the female usually just over 50% The lower proportion in the female is due to the relatively greater fat content As fat is anhydrous and contains no salt the cation content of the two sexes expressed on a body weight basis also shows characteristic differences In one series of observations the mean exchangeable sodium in the male was 42 1 m-equiv /Kg and in the female 39 6 m-equiv /Kg (Miller and Wilson 1953) and other series have shown a similar difference though the range is always wide (Forbes and Perley 1951) The exchangeable potassium is usually considerably greater in the male due not only to the lower fat content but also to the greater muscular mass Average figures for exchangeable potassium are in the male 46 8 m-equiv /Kg and in the female 40 7 m-equiv /Kg (Edelman *et al* 1952b) but here again there is a considerable scatter in the normal values In health there is a fairly constant relationship between the amounts of exchangeable sodium and potassium in the body The mean

ratio $\frac{\text{exchangeable sodium}}{\text{exchangeable potassium}}$ in males is 0 91, and in *females* 1 02 (Moore Edelman Olney James Brooks and Wilson 1954) Measurements of exchangeable chloride have usually been made with the isotope ^{82}Br, which is for the most part distributed in the same way as chloride throughout the body In a recent investigation the total body chloride is reported as approximately 32 m-equiv /Kg in healthy young adult men and 26 m-equiv /Kg in women (Reid, Forbes Bondurant and Etheridge, 1956) Some of the changes in body composition caused by disease have also been investigated and will be described later

The isotope dilution method is not only of value in ascertaining the initial body composition before surgery Interval determinations may be made while the patient is in hospital and the changes revealed in this manner usually are in good agreement with those shown by metabolic balance techniques (Wilson Olney Brooks Myrden Ball and Moore, 1954b) Furthermore the observations may be extended far out into convalescence after the patient's discharge from hospital and the long term changes studied in this way

Certain additional information may be deduced from the measurements of total body water and exchangeable potassium When the water content of the body is known the fat content may be calculated on the assumption that lean tissue contains about 73% of water (Rathbun and Pace, 1945)

$$\% \text{ Fat} = 100 - \frac{\% \text{ water}}{0\ 73}$$

Clearly, the assumption regarding the extent of hydration of lean tissue is not justified in many pathological conditions particularly in the presence of cardiac and renal disease On the other hand in the majority of cases these calculations though not precise offer a first approximation of changes in body fat in the presence of disease The problems associated with estimations of this nature have been fully reviewed (Moore Haley Bering Brooks and Edelman 1952 Keys and Brožek 1953)

The distribution of potassium in the body is extremely uneven Of the total only about 2% is in the extracellular space and only 0 7% in the blood plasma The bulk of the potassium is in the cellular mass of the body mostly in the muscles As will be described later, a differential loss of potassium may develop under certain circumstances but in general apart from periods of acute stress and certain diseases changes in total exchangeable potassium are related to changes in cellular mass in the body

Isotope dilution studies cannot be readily repeated more often than once a week, so that the immediate day to day changes after trauma

are best followed by metabolic balance studies It is important to emphasize the dynamic character of the biochemical changes seen after trauma and closely sequential observations are essential to reveal the rapidly altering picture as each day passes The technique of these studies in surgical patients has been fully described elsewhere (Moore and Ball 1952) Balances of nitrogen potassium and sodium have been extensively investigated in a wide range of different conditions and will be described in detail as sufficient information is now available for the construction of an average picture Some measurements of chloride balance have been made and will be mentioned briefly Less extensive observations have been made of phosphorus sulphur and calcium metabolism (Cuthbertson 1942 Reifenstein Albright and Wells 1945 Eliel Pearson and White 1952)

It is important to emphasize the advantages that accrue from a combination of the measurements of body composition and of metabolic balance The latter affords only a limited picture of the biological changes in progress and is liable to a considerable cumulative error On the other hand the body composition measurements reveal the background on which these changes are imposed It is thus possible to elucidate the roles played by previous disease and by trauma and to show how abnormalities in body composition alter the response to injury

In all cases great importance should be attached to the accurate daily recording of body weight as this yields information of the greatest value in relation to the metabolic balance changes and the isotope dilution measurements If body water and lean tissue remain constant while weight changes the alteration in weight is clearly due to a change in the fat content of the body the fat being anhydrous The assumption of a lean tissue coefficient of 30 for nitrogen (Moore and Ball 1952) permits calculations of the changes in lean tissue in terms of the nitrogen balance

Changes in the plasma concentration of sodium potassium and chloride frequently develop after trauma These are of great interest and can be studied satisfactorily only if frequent often twice-daily observations are made

In an effort to elucidate some of the mechanisms at work in initiating the response to injury studies have been made of changes in the function of certain endocrine organs The adrenal cortex especially has been studied and the investigations have been based mainly on eosinophil counts and on the urinary excretion of 17 ketosteroids ketogenic steroids and 17 hydroxycorticoids (Forbes Donaldson Reifenstein and Albright 1947 Reddy Jenkins and Thorn 1952 Norymberski Stubbs and West 1953) Attempts have been made to estimate the plasma concentration of these hormones (Nelson Samuels Willardson

and Tyler 1951) and this work is described later The part played by the other endocrine organs has so far been less fully investigated but recent studies have been directed especially to the anterior and posterior lobes of the pituitary and to the thyroid

The accurate assessment of the severity of the injury that sets in motion the metabolic changes is clearly of considerable importance but it nevertheless presents great difficulties A loose, semi quantitative scale is all that can be attempted Thus a third-degree burn of 25% or more of the body surface is at the top with scale 10 Multiple wounds penetrating wounds of the chest and abdomen major fractures are scale 9–7 The type of extensive multivisceral operation employed for cancer falls in a similar range Scale 5 is represented by ordinary, major, anastomotic gastro intestinal surgery such as colectomy or subtotal gastrectomy Cholecystectomy and hysterectomy may be scale 4–3 The simpler and minor procedures scale on down to 2, and an ankle sprain and its operative counterpart may be regarded as scale 1 Such an approximate expression of the magnitude of trauma as a biological stimulus to elicit a metabolic response is essentially a guess based on a consideration of the tissue involved blood loss, tissue necro sis infection, duration of trauma and pain

Metabolic Changes following Trauma in the Healthy Adult

In the majority of cases following a moderately severe injury of about scale 6–7 in a healthy adult, four fairly distinct phases of reaction may be distinguished (Moore, 1953) These may be described as follows

I Rapid catabolism of lean tissue and fat
II Decline of catabolism and preparation for anabolism
III Spontaneous anabolism of lean tissue
IV Restoration of fat

The features that characterize them will be described in due course, but in the first place it is essential to consider briefly any changes that may be associated with the anticipation of trauma

Pre-operative Features Apprehension is present in varying degree in any healthy individual before a surgical operation and may produce some limited metabolic changes On the evening prior to operation there is usually dietary restriction in nitrogen intake with a resultant small negative balance for the 24 hours prior to surgery Occasionally the eosinophil count may drop before operation This is frequently attributed to anxiety but the exact mechanism is open to some doubt especially when pre operative sedatives such as morphine have been injected The extent to which emotional stress and apprehension may activate the adrenal glands has been the subject of recent investigations

(Hill *et al* 1956) While anxiety may sometimes increase adrenal cortical secretion it is improbable that anticipation of the event alters significantly the subsequent response to trauma and the metabolic changes seen after a planned operation or after the unexpected receipt of a soft tissue injury are essentially similar

Phase I This stage is characterized clinically by all the reactions to the effects of an acute injury Haemorrhage pain and fear are clearly factors of importance Other features are the tachycardia and slight pyrexia which persist for two or three days in the complete absence of any infection

It is important in relation to the metabolic changes to recall the condition of the wound at this time It has as yet no tensile strength and if the sutures are cut it readily falls apart The characteristic microscopic changes are the formation of a fibrin coagulum in an accumulation of extracellular fluid blood cells and tissue debris There is an invasion of phagocytic cells and polymorphonuclear leucocytes whether or not infection actually occurs

The metabolic features at this early stage are essentially associated with the breakdown of lean tissue and fat retention of water and salt and a characteristic endocrine response

The body weight drops quickly to an extent greater than predicted from the amount of tissue excised and from changes in nitrogen balance and body water This indicates the rapid utilization of body fat There is a relative oliguria on the day of operation and for the succeeding day or two Excess water given at this stage is retained in the body and excreted only after a few days This water retention occurs even with no sodium intake A failure to lose weight after an operation always indicates water retention

The urinary nitrogen excretion is considerably increased Even with no nitrogen intake it becomes larger than it was pre operatively on a basal diet This quantitative increase in excretion rate is characteristic of the response to extensive trauma Since there is usually a minimal nitrogen intake during this first phase the source is presumed to be the general body protein of which the greatest part lies in skeletal muscle The rate of nitrogen excretion is usually at its height on the day of operation and on the succeeding day Thereafter it decreases stepwise Occasionally a so-called delayed peak nitrogen excretion is seen but this is exceptional after an operation involving only soft tissue trauma In either event since there is little or no nitrogen intake in this phase a negative balance results At its height the negative balance after a trauma of the degree being considered may be about 10–15 g a day The excreted nitrogen is mainly in the form of urea and ammonia which together account for 85% or more of the nitrogen in the urine

Potassium excretion shows a loss on the day of operation of about

50–75 m equiv, which thereafter is steadily reduced Again since there is ordinarily no intake at this time there is a negative balance The potassium nitrogen ratio of the negative balance at this time is characteristically 5 m equiv /g or more indicating a mobilization of electrolyte disproportionate to cell matrix, where the ratio commonly is between 2 5 and 3 5 m equiv of potassium per g of nitrogen

The excretion of phosphorus and sulphur is increased at this stage and negative balances for these substances develop A study of the sulphur nitrogen ratio of the total amounts excreted in excess indicates that the substance being catabolized is apparently mainly skeletal muscle as suggested above This conclusion is in general supported by the phosphorus nitrogen ratio (Cuthbertson 1942)

The urinary sodium excretion on the day of operation is almost negligible The intake also is extremely low unless saline is given intravenously The loss of sodium in the sweat and faeces is small and the usual net metabolic effect is no exchange with the environment If, however there is considerable drainage of fluid from the wound a negative balance may result Chloride metabolism usually runs parallel to that of sodium

The caloric intake by mouth at this stage is usually quite low or zero Approximately 150–400 calories a day may be supplied by intravenous dextrose solutions Attempts have been made to increase the caloric intake by supplying other materials such as alcohol fat or protein hydrolysates but their utility in this early period has not been convincingly demonstrated

Definite changes in blood chemistry develop during this stage The concentration of sodium in the plasma shows a distinct fall With an extensive injury (scale 6–7) the sodium concentration may fall from a normal pre operative value of 142–140 m equiv /L to about 137–135 m equiv /L This drop is part of the normal physiological response it does not in any way endanger the survival of the patient nor is it harmful in itself It occurs despite extreme renal conservation of sodium and is not due to sodium loss from the body Indeed the fall is often seen while sodium is being freely administered There is a similar drop in plasma chloride concentration This also occurs without any loss of chloride from the body By contrast the serum potassium concentration may rise after an extensive injury at a time when a large renal excretion of potassium is in progress The blood urea nitrogen is often elevated and the fasting blood sugar may be increased These changes in the blood plasma in the immediate post operative period are of great theoretical interest and may be of extreme practical significance in severely ill patients with concomitant extrarenal losses or with cardiac or renal disease

The eosinophil count drops rapidly during the operation and is often

at or close to zero by the time it is completed It remains low for two to five days depending on the magnitude of the operation the continuance of post-operative pain or the superimposition of abnormalities such as infection If there are no major complications the eosinophil count then starts to rise

Urinary excretion of 17 ketosteroids shows a sharp upward rise on the day of operation This however may last only one day and thereafter the excretion returns to a normal or below normal level (Venning Hoffman and Browne 1944 Venning 1950 Bennett and Moore 1951) The excretion of 17 hydroxycorticoids and of 17 ketogenic steroids shows a conspicuous rise on the day of operation and for several days thereafter descending in a stepwise fashion to the pre operative level (Norymberski *et al* 1953 Thorn Jenkins and Laidlaw 1953 Moore, Steenburg Ball Wilson and Myrden 1955)

Phase II In a patient subjected to moderately extensive trauma (scale 6–7) this phase of convalescence begins about the fourth day and lasts two or three days Clinically there is an improvement in appetite an increase in spontaneous physical activity and a developing interest in the surroundings The wound usually becomes free of acute pain when no strain is applied Its tensile strength is increasing There is considerable fibroblastic proliferation new intracellular substance is laid down, and epithelium is formed

The metabolic changes at this stage represent the turn of the tide The outflow of the end products of tissue breakdown is checked and the body is preparing for the reconstruction of the lost lean tissue The weight continues to fall but the loss bears a closer correlation to water and lean tissue changes and fat utilization is much less prominent The urine output usually increases and may actually exceed the intake for a day or two There may be a further sharp weight loss during such a water diuresis

The nitrogen-excretion rate in the urine is now *definitely* lower Since a full diet has not yet been resumed a strongly positive nitrogen balance is rarely seen during this phase There is usually an approximately zero balance with a gradual trend towards the positive side It is therefore not the balance but the sharply decreased urinary nitrogen excretion rate which is the characteristic metabolic alteration of the second phase This change may be dramatic as for example in cases *where in a period of 48 hours the urinary nitrogen-excretion rate is* reduced from 15 g to 5 g a day in the face of unchanged nitrogen intake urine volumes and blood urea This alteration indicates a cessation of lean tissue destruction and a readiness to start anabolism

As potassium is gradually introduced into the diet the urinary excretion rate is sharply reduced (as low as 5–15 m-equiv a day) The result is a positive potassium balance—in contrast to nitrogen where

retention develops more slowly The potassium nitrogen ratio of the negative balance in phase I was high but a reverse of this phenomenon is now seen, namely a positive potassium balance during a zero or only weakly positive nitrogen balance After two or three days potassium excretion is again increased as intake improves until characteristically at the end of this phase the patient is showing only a slight gain of potassium The result is a restoration to the body of most of the potassium initially lost in excess of nitrogen

The sodium picture is the inverse of that of potassium As the sodium intake becomes progressively larger as a result of increasing diet, the sodium excretion is disproportionately augmented The result is a diuresis of sodium the extent of which is directly proportional to pre vious sodium loading In general the available information indicates that the chloride metabolism follows the pattern of sodium

The caloric intake characteristically rises in a stepwise fashion As the patient has more interest in food he increases his diet but during this phase it usually does not return to normal

The plasma sodium and chloride concentrations are rising to normal values during this stage and the plasma potassium if previously ele vated falls to normal These changes occur despite the increased excre tion of sodium and chloride in the urine and the retention of potassium

The eosinophil count rises steadily and may even reach a level con siderably above the pre operative values It is interesting that this over shoot may last only one day or a fraction of a day and then the eosino-phils decline to normal The excretion of 17 ketosteroids is normal during this period The excretion of 17 hydroxycorticoids falls and reaches the pre operative level towards the end of this phase

Phase III This is associated with the beginning of reconstruction of the tissue burnt during the catabolic phase and commonly begins between the seventh and tenth days after an extensive injury A generous dietary intake is essential If diet is not increasing rapidly towards normal at this time convalescence is retarded and there is a failure to gain weight strength and vigour It is noteworthy that wound healing commonly proceeds to completion despite prolonged dietary interruption and despite negative nitrogen balance due to post operative starvation Return of strength and clinical recovery however do not occur under such circumstances and convalescence is incomplete Up to this point diet is not needed for convalescence or wound healing now it becomes essential for survival

The characteristic clinical features during this stage are increasing strength and a return of appetite The latter indeed may become con siderably larger than normal There is greater physical and mental activity The tensile strength of the wound has increased The wound remains red and grows above the surrounding tissue It still clearly

carries a high biological priority as shown by the common occurrence of complete healing in the absence of dietary intake as mentioned above The local activity in the wound is apparently related to deposition of intracellular substance such as collagen

The pre-eminent metabolic feature of this period is the restoration of lean tissue which takes place over several weeks The other changes are not particularly remarkable

There is a weight gain which correlates closely with that predicted from nitrogen balance indicating that lean tissue is being reformed and that fat gain is not prominent Usually there is a sustained positive *nitrogen balance in the range of 3–5 g of nitrogen per day per 70 kg* of body weight This is the convalescent normal rate of anabolism and it cannot be increased by forced feeding The caloric intake must be at a high level to maintain this nitrogen anabolism and the ratio of non protein calories to grams of nitrogen in the diet should be 100 or higher Anabolism is ready to start after a few days of the second phase The provision of a full intake allows it to begin

The potassium balance is only weakly positive yet adequate to account for a normal intramuscular potassium nitrogen ratio of about 2 7 m equiv /g of nitrogen By ordinary methods this positive potassium balance is scarcely discernible and is much smaller than the spectacular positive potassium balance seen during phase II The increase in potassium in the body throughout this long phase is most convincingly studied by serial measurements of total exchangeable potassium which clearly demonstrate the incorporation of potassium in the restored lean tissue The sodium and chloride metabolism is essentially normal There may be wide daily swings but the average balance for any period of a few days is close to zero There is no dis turbance of water excretion and normal urine volumes are maintained

Caloric intake as mentioned above must be sustained in the region of 2000–3000 calories per day in order to maintain the maximum rate of protein synthesis This synthesis presumably occurs chiefly in skeletal muscle

The concentrations of the different constituents of the blood plasma are all normal throughout this phase The eosinophil count is likewise normal The excretion of steroids derived from the adrenal cortex is usually at a low level

Phase IV The patient has now been discharged home and after adding an amount of nitrogen to his body commensurate with that previously lost he enters into the fourth phase of convalescence which may last many weeks or months It is characterized by a return of full body weight and function During the fat gain phase the patient usually returns to work but if this imposes a high caloric requirement, there may be a considerable delay in the full body fat. Clearly

the provision of an adequate diet is necessary for the development of this phase *The wound at this time flattens broadens and gradually turns white*

The eosinophil count has been normal and continues so The steroid excretion previously often slightly depressed now returns to normal

The completion of the fat gain phase is shown by the return of body weight to normal, and at this time *metabolic convalescence appears to be complete*

The Effect of the Severity and Nature of the Trauma

The features that have been described are applicable to the response seen in an adult of normal body composition subjected to moderately extensive trauma involving soft tissue only (scale 6–7) Certain differ ences are seen in the response in healthy subjects depending on the *severity and nature of the injury*

Minor Trauma

With a lesser degree of trauma for example an appendectomy or simple repair of an inguinal hernia (scale 2 or 3) the changes are smaller both in degree and in duration The first phase of accelerated catabolism may last only one or two days The negative potassium balance may be restricted to the day of operation and sodium retention is not marked *The intermediate phase II is scarcely noticeable* the patient rapidly passing into the third phase of lean tissue reconstruction A small amount of fat oxidation usually occurs Changes in blood chemistry are not conspicuous but if frequent careful measurements are made of plasma sodium concentration a small dip in the curve of 2–3 m equiv /L can often be detected Water retention on the day of operation and a diuresis on the following day are usually apparent The eosinophil count drops—usually but not always to zero—and then rapidly rises *There is little significant change in the excretion* of 17 ketosteroids The excretion of 17 hydroxycorticoids is elevated for the 24 hours following operation but thereafter rapidly falls to normal

It is apparent that with a *small soft* tissue injury the same type of metabolic response is seen as in the more severe cases The quantita tive changes are however considerably smaller and the phases of convalescence are much shorter

Major Soft tissue Trauma

Multiple wounds of soft tissue and extensive visceral injuries (scale 8 or 9) produce in a healthy subject a more prolonged catabolic phase *as might be anticipated The rate of lean tissue* and fat catabolism is brisker and there is consequently a greater loss of weight The changes in plasma concentrations are more conspicuous The urinary excretion

of steroids is increased over a longer period The reparative processes concerned with the restoration of the catabolized tissue are prolonged as the result of the greater destruction of lean tissue and fat during the acute phase

In two types of severe injury spectacular metabolic responses are commonly seen namely major fractures and thermal burns of the body surface They are worthy of more detailed consideration

Bone Injury

There is considerable evidence to suggest that bone trauma elicits a much more vigorous metabolic response than one would predict solely on the extent of the injury were only soft tissues involved (Cuthbertson 1932 Howard 1944 Armstrong 1944) Recent work further corroborates this (Moore *et al* 1955) Certain features demand special attention The nitrogen-excretion rate is exceptionally high and the peak rate is often not attained until a few days after the fracture—a feature by no means common in soft tissue surgery when the maximum excretion usually (but not always) occurs on the day of operation In many fracture cases caloric intake is unimpaired and the response is usually studied in vigorous young adults While these are often factors of importance the magnitudes of nitrogen excretion and negative balance far exceed what would be anticipated The total daily excretion of nitrogen may on occasion be as high as 40 g Negative balance rates of between 15 g and 20 g are often observed and may be maintained for several days at this high level The duration of the catabolic phase is unduly prolonged In one case of multiple fractures the nitrogen balance remained negative for 28 days in spite of an unimpaired intake In a case of fractured femur it was negative for 22 days even though the caloric intake was exceptionally high

The potassium balance similarly shows a more prolonged negative phase though it is characteristically shorter than the period of negative nitrogen balance

There is a steady and prolonged weight loss after a major fracture and calculations show that this is due to the burning of both fat and lean tissue

In contrast to the major metabolic disturbances described above the changes in eosinophil counts and in urinary steroid excretion are not unduly spectacular in comparison with what is seen in soft tissue injury The eosinophils drop to zero immediately after the injury but rapidly rise to a normal level and may reach above normal heights within seven to ten days after receipt of the fracture—that is at a time when the negative nitrogen balance is still in full swing The excretion of 17 ketosteroids is elevated for about the first two days and of 17 hydroxy corticoids for several days longer Neither of these indices of adrenal

function necessarily continues elevated for the whole duration of the prolonged catabolic phase

Burns

The metabolic response to extensive thermal burns presents several unusual aspects which have been fully reviewed (Peters 1945 Moore Langohr Ingebretsen and Cope, 1950) The more important features only are summarized in this section They fall naturally into three phases, comprising respectively the first three to four days the succeeding two weeks and the remainder of convalescence The precise duration of each phase may vary considerably with the circumstances, but the essential metabolic sequence is usually constant

The First Three to Four Days During this period there is often a positive nitrogen balance due to plasma therapy and reduction of urinary excretion due to oliguria Clearly this positive balance does not indicate tissue synthesis There is a remarkably transient potassium loss phase lasting only two to four days and followed by a rapid restoration to positive balance as soon as moderate potassium intakes (over 50 m equiv /day) are provided There is a large positive sodium balance provided the patient is given enough sodium to permit survival This sodium accumulation is partly due to renal conservation and partly to the obligatory sequestration of large amounts of sodium in the wound oedema (Cameron 1945 Cope and Moore 1947) The volume of this obligatory oedema approximates 7% of the body weight in burns over 25% of the surface area It will be readily appreciated that during this phase the burnt patient shows a gain in weight There is usually an increase in urinary steroid excretion and a fall in eosinophil count as after any form of trauma Haemolysis and renal damage with consequent azotaemia may become apparent at this stage The extent of the extrarenal loss of fluid protein and electrolyte through the burnt skin depends largely on the nature of the burn If the surface is heavily charred the area remains dry On the other hand a large loss may occur as a result of a scald or second-degree burn

The Succeeding Fourteen Days The nitrogen balance now becomes sharply negative provided that renal excretion is adequate the rates (urine and wound) may be as high as 30–45 g a day This phase of excessive nitrogen excretion may begin at any time after the third day and lasts at least through the second week in extensive burns it may last a month or longer The potassium balance is commonly positive during this phase A sodium diuresis develops at about the third to sixth day as the wound oedema is reabsorbed In patients with good renal function this is readily discernible by the increased urine volume and greatly increased sodium content In patients with renal damage and consequent diminished excretory ability retention of this fluid re

absorbed from the wound may produce venous congestion and pulmonary oedema The burnt skin begins to slough and the extrarenal losses increase abruptly Anaemia and sepsis frequently develop During this stage there is a large and rapid loss of weight due to the excretion of the oedema fluid and the greatly accelerated catabolism The urinary steroid excretion is low

The Remainder of Convalescence The metabolic balance gradually moves towards anabolism The urinary nitrogen-excretion rate is gradually reduced so that positive balance is achieved with intakes in the 15/20-g range Epithelial proliferation becomes evident around the wound edges, grafts take readily and the anaemia improves The loss through the wound of nitrogen and electrolytes is reduced The urinary steroid excretion rises towards normal The potassium balance is positive and the sodium balance is zero A high caloric intake is essential at this stage If there is a failure to maintain adequate nutrition convalescence is stalled and the patient makes little progress Skin grafts fail to take, destructive sepsis may develop and the patient eventually succumbs

The metabolic changes associated with an extensive burn are of great theoretical interest They illustrate the type of response that may be anticipated as a result of a particularly severe type of injury associated with much inflammatory oedema

Excessive Extrarenal Loss

Convalescence in a previously healthy patient is delayed or halted by excessive loss of water crystalloids and protein from wounds or the gastro-intestinal tract Several litres of fluid a day may escape from an upper gastro intestinal fistula by aspiration through a Miller Abbott tube or from profuse diarrhoea Although gastric juice and mucus contain considerable and variable quantities of sodium (5–125 m-equiv / L) post-operative loss is most sudden and profound from pancreatico duodenal and biliary (130 m-equiv sodium/L) fistulae from which several litres of sodium rich fluid a day may be lost In profuse diarrhoea with much mucous secretion the concentration of sodium may be even higher (350 m-equiv /L)

Although extrarenal losses of potassium are not usually great from the upper intestinal tract watery stools contain up to 70 m equiv /L. More commonly severe potassium depletion occurs where long term extrarenal loss of electrolytes as from gastric aspiration or vomiting has been replaced by sodium and chloride alone In this way perhaps a third of the body store of potassium can be lost even when sodium and chloride reserves are normal The loss of potassium in the urine increased after operation continues even in face of the great deficiency in body reserve this contrasts with the body s hoarding of sodium The

starvation consequent on gastro intestinal complications causes a further loss of caloric intake and a continuance of heavy nitrogen and potassium losses

Successful management of excessive extrarenal losses depends among other things, on early recognition of the problem an accurate estimation of the previous and current depletion and their replacement by the most satisfactory route and vehicle Detailed consideration of the principles underlying such treatment is given in Chapter 2

The Metabolic Response in Relation to Previous Health and Body Composition

So far the description of the metabolic reactions has been confined to patients in good health before the receipt of different types of injury In other words the initial body composition was normal and the subsequent subtractions and additions have been superimposed on a normal structure Many types of chronic disease lead to body wasting with a loss of lean tissue and fat (McCance and Widdowson 1951) Isotope-dilution studies show in these subjects a gross distortion of body composition namely an increase in the proportion of water a decrease in exchangeable potassium and an increase in exchangeable sodium (Moore *et al*, 1954) The decrease in potassium which is almost entirely an intracellular ion is related to the loss of lean tissue Clinically these changes may be observed in any disease process which has led to a deterioration in general health They are often seen in pronounced degree in patients with disease of the alimentary tract which has interfered with the ingestion digestion and absorption of food In these circumstances the total body water measured with deuterium oxide may be as high as 75% of the body weight in male patients and in females it may reach 70% The ratio total exchangeable sodium/exchangeable potassium is also grossly disturbed and may be 1 5 or even higher Examples of this type of change are shown in Fig 1 It is not surprising that these gross alterations in body composition affect the biochemical reactions after an operation or other form of trauma

Old and wasted patients present a modified response to operation in general the catabolic phase is depressed and shortened Nitrogen excretion falls to or is maintained at, a few grams a day with a potassium nitrogen ratio of less than 5 m-equiv /g The expected loss of potassium and retention of sodium is likewise diminished In contrast the adrenal cortex appears to react as in the normal and healthy patient there is evidence that the urinary excretion of 17 hydroxycorticoids is increased for several days following trauma in the wasted carcinomatous or old patient and that the adrenal cortex is readily responsive to post operative infusions of corticotrophin Patients with extensive carcinomatous involvement may even have an exaggerated post operative

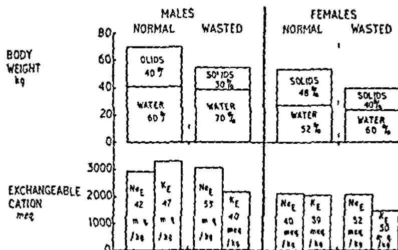


Fig 1 An example of the normal body composition in the adult male and f male and of the changes that may occur as a result of wasting disease

excretion of adrenal corticoids It is evident therefore that the modifi cations of the various elements of the metabolic response may be in both directions and even in any one individual the range of responses is great and difficult to predict This is illustrated by the balance observations of ten patients very similar in clinical presentation with pyloric stenosis complicated by alkalosis (Black and Jepson 1954 Davies Jepson and Black 1956) Using post-operative retention as an index it was found that three were sodium-depleted five potassium depleted and four chloride-depleted All were subjected to the same type of partial gastrectomy and the cumulative balances reflect the variation in individual response these ranged for nitrogen from − 29 to + 92 g, calcium from 0 7 to 6 0 g phosphorus − 8 to + 2 6 g sodium − 309 to + 1762 m-equiv potassium − 248 to + 808 m-equiv and chloride − 244 to + 1890 m equiv It is evident that although generalizations can be made each patient is a separate problem in quantitative meta bolic behaviour and this is particularly true of the depleted patient

Response to a Second Operation

A second operation closely following one of equal magnitude evokes considerably less metabolic change This is reflected both by the varia tions in plasma concentrations of sodium potassium and chloride and by the urinary excretion of these substances in particular the negative nitrogen balance is less evident and lasts for a shorter period This damping down of the response holds for the urinary excretion of ketosteroids ketogenic steroids and total 17 hydroxycorticosteroids

Cardiovascular Disease

The increasing frequency of operations for the relief of valvular heart disease and of operations for other conditions in patients with heart disease has drawn attention to the special metabolic features that may develop in such circumstances A recent investigation of the changes associated with mitral valvulotomy has shown that such patients though clinically free from oedema and brought into the best possible condition by medical treatment before operation, usually show definite abnormalities in body composition (Wilson, Edelman, Brooks Myrden Harken and Moore 1954a) These are an excess of water and sodium and a decrease in potassium—features already mentioned as typical of any type of wasting disease

In the pre operative period in the more severely ill patients there has usually been salt restriction and administration of mercurial diuretics After operation many of the metabolic features are those seen in de pleted patients The catabolic phase with respect to nitrogen is not unduly conspicuous and the adrenal steroid excretion in the urine may not be greatly increased On the other hand disturbances of salt and water metabolism are often extremely marked In the immediate post operative period there is a considerable fall in the serum sodium con centration from about 140 m equiv /L to 130 m-equiv /L or lower At the same time the serum potassium rises Water retention readily develops while the sodium intake is restricted to cover only that lost at operation and in the chest-drainage fluid During this period the patient is thirsty and may consume a large quantity of water On the other hand there is definite oliguria during the two or three days after operation so that the total body water rises and weight may be gained Diuresis of all the excess water may not occur until a week after opera tion These are the outstanding abnormalities of metabolism seen in patients with valvular heart disease undergoing operations They are clearly an exaggeration of the tendencies already noted in operations on patients with healthy cardiovascular systems

The large decrease in serum sodium concentration has occasioned much discussion as to mechanism and significance In the majority of cardiac patients it is not due to the loss of sodium from the body as this has been adequately restored The fall may be diminished by severely restricting fluid intake in the post operative period so that the total body water does not rise Even in these conditions there is still a substantial fall in serum sodium concentration after operation Usually the fall is only transient, lasting four or five days before it begins to climb towards normal It is certainly not an indication for the adminis tration of hypertonic saline which will only further expand the extra cellular fluid and increase the load on the heart In a few patients the

serum sodium concentration may remain persistently low after operation and in them a deficiency of both sodium and potassium may be present This condition is usually associated with a long-continued low sodium diet repeated administration of mercurial diuretics in patients not markedly oedematous and inadequate replacement of salt lost as a result of operation The serum sodium concentration will not return to normal until the deficiencies of electrolytes are restored In the post operative care of these patients it is important to remember how readily water retention may occur leading to a gross imbalance between the amounts of water and sodium in the body Features of water intoxication may readily develop in such circumstances

Other Factors Contributing to the Metabolic Response to Surgery

There are many variables concerned with an operation performed under anaesthesia which must be considered when we survey the over all metabolic response Obvious variables are the amount of tissue traumatized the length of the operation apprehension anaesthetic agents and premedication body cooling hypotension in addition in the convalescent period there is starvation immobilization fever infection and pain Not all of these factors have been accurately studied but some information is available Siker Lipschitz and Klein (1956) established that pre anaesthetic saline atropine morphine and scopolamine produced no change in the blood levels of the free 17 hydroxy corticosteroids Pentothal induction however reduced a figure of 12 μg /100 ml to 6 It is known that during major operations the plasma level of circulating 17 hydroxycorticosteroids rises although the modifying effect of the various anaesthetic agents is unknown that an anaesthetic is not an essential component is clearly shown by the development of the metabolic response where no anaesthetic has been given for example after a fractured femur When hypothermia is used the free-corticoid levels in the peripheral blood stay constant even with extensive surgical trauma (Bernhard McMurrey Ganong and Lennihan 1956) There is simultaneously a lessened production of the adrenal steroids as shown by estimation of samples of adrenal venous blood and a diminished conjugation of these compounds in the liver Normal adrenal production promptly returns on warming Wynn (1956) has shown that *during induced hypothermia in men and dogs exogenous* fructose and glucose are more slowly metabolized and the plasma sodium level may fall Haemorrhage is associated with all kinds of open and closed trauma and it is suggested by Flear and Clarke (1955) that loss of blood and an inadequate circulating blood volume are major factors in the causation of post traumatic metabolic changes It has long been recognized that haemorrage alone produces an increased

excretion of nitrogen Haemorrhagic shock at normal body temperature causes a rise in corticoid concentration in the venous adrenal blood so that the total output does not fall Anxiety fear and tension of operation very profoundly affect fibrinolysis and there is some suggestion that these emotions may cause a rise in plasma corticoids

Numerous metabolic studies have shown that various infections and fevers lead to an increased excretion of nitrogen during the acute phase (Peters 1944) This has been described in association with typhoid fever meningitis malaria pneumonia and other types of febrile illness (Shaffer and Coleman, 1909 Barr and Dubois 1918 Grossman Sappington Burrows Lavietes and Peters 1945 Howard Bigham and Mason 1946b) The protein catabolism is apparently similar to that seen after trauma and its severity and duration are dependent on the nature of the infection Identical metabolic changes are also observed as a part of the inflammatory reaction caused by the injection of sterile irritant substances (Madden and Clay 1945) On the other hand fever alone will not account for the metabolic reaction to injury which is often seen in patients who run an entirely afebrile course Infection and fever however clearly may be accessory factors exaggerating the metabolic response to trauma

Simple starvation obviously leads to a negative nitrogen balance and it is pertinent to inquire to what extent the anorexia present after an extensive injury contributes to the metabolic pattern There are however certain clear differences between the post operative and the starving patient (Cuthbertson 1942 Howard Bigham, Eisenberg Wagner and Bailey 1946a Moore and Ball 1952) Operation and starvation both lead to a negative nitrogen balance With starvation the nitrogen excretion is about 10 g /day in a man of average size Much higher excretion rates may be seen after severe trauma in a patient receiving no nutriment Furthermore addition of food rapidly reverses the negative balance in starvation but forced feeding with high-calorie diets does not appreciably spare the body nitrogen at the height of a vigorous protein-catabolism reaction Turning to sodium there is an obvious contrast with the post operative patient At the beginning of starvation there are large urinary losses and renal conservation of sodium does not begin until after about three to four days After operation there is immediate retention of sodium even in the presence of a large intake The potassium loss in starvation is much more closely related to the nitrogen excretion and the gross disturbances of potassium nitrogen excretion ratio commonly seen after trauma do not develop in starvation While the diminished caloric intake after an injury has a great influence on the metabolic balance it is definitely not responsible for the conspicuous catabolic reaction

The activity of a patient is inevitably restricted after the receipt of

trauma particularly in the case of fractures when a plaster cast has been applied This aspect has been fully studied (Deitrick Whedon and Shorr 1948) A loss of calcium and phosphorus is conspicuous in such circumstances Smaller losses of nitrogen potassium and sodium also occur but are only a fraction of those seen after trauma Clearly the enforced rest in bed cannot account for the dramatic metabolic changes associated with injury Finally it is worth noting that after a period of complete bed rest a transient negative nitrogen balance may again be noted on resuming activity (Browne Schenker and Stevenson 1944) This is commonly observed on the first day of walking about the hospital ward after a minor surgical operation such as appendectomy

While the factors considered above may all contribute to a small extent to the large metabolic disturbance observed after the infliction of a severe injury it is clear that the wound itself must play the greatest part The connecting links between the wound and the biochemical changes are still uncertain

Endocrine Factors in the Metabolic Response

The means by which the widespread chemical and physical changes occur in cells and tissue fluids after injury remains obscure Harris (1951) has suggested that the damaged tissue stimulates the hypothalamus which in its turn augments corticosteroid production The adrenal corticosteroids are known to influence the cell enzyme systems either directly or via their substrates and co factors (Thorn *et al* 1953) This schema is without doubt oversimplified and it would probably be a more accurate conception to say that the body response to injury is greatly modified by the hormonal response rather than initiated by it An understanding of the part the endocrine glands play in response to trauma has been greatly limited by available techniques for their estimation particularly in regard to the corticosteroids Biological tests have been used for the analysis of gluco and mineralo-corticoids (Dorfman 1954) but their application must of necessity be limited to those substances which show biological activity Paper chromatography has not been sufficiently developed to allow routine laboratory assays In the past few years however chemical methods have been developed for plasma (Nelson and Samuels 1952) and urine (Nelson and Samuels 1952 Reddy *et al* 1952 Norymberski *et al* 1953) assay of 17 hydroxycorticosteroids of these Norymberski s assays of ketogenic and total 17 hydroxycorticosteroids seem the most comprehensive In addition to the direct estimation of adrenal hormones indirect indices have been used such as fluctuations in the eosinophil count and the histochemical examination of the adrenal glands after death or corticotrophin stimulation

Plasma Concentration of 17-hydroxycorticosteroids

Evidence has accumulated in recent years to suggest that 17α hydroxycorticosterone (hydrocortisone Kendall s compound F) and to a much lesser extent corticosterone are quantitatively the most important hormones secreted by the adrenal cortex Additional steroids occur in varying amounts in perfusates of adrenal cortex Simpson, Tait and Bush (1952) have demonstrated the presence of aldosterone in adrenal gland extracts and urine The plasma concentrations of corti costeroids are usually estimated in the free rather than conjugated form and some variation is reported in the expected plasma level, which may be partly due to the small amounts of available steroid for assay and the inherent difficulties of a technique involving chromatographic separation The resting levels of free steroid for adults are given as 4–10 μg /100 ml plasma (Franksson, Gemzell and von Euler 1954) 13 μg $\pm$ 6 μg (Bliss Sandberg Nelson and Eik Nes 1953), 3–22 μg /100 ml (Sandberg Eik Nes Samuels and Tyler, 1954) and an average of 11 μg by Klein, Papadatos Fortunato and Byers (1955) Pre operative apprehension and premedication do not generally *affect this level significantly* but *it rises sharply with the onset of* the anaesthetic induction There is no evidence for a preliminary *fall in plasma level due to withdrawal of existing circulating steroids* into the damaged area, a mechanism which it has been suggested might act as the primary pituitary stimulus Increase is first detected in free steroids (Klein *et al* 1955) followed by the conjugated compounds The maximal operative level of free steroid was found to be 31 4 $\pm$ 1 9 μg /100 ml by Franksson *et al* (1954) while Klein *et al* (1955) found the average rise in nineteen patients to be 51 μg for free and 21 μg for conjugated steroids The plasma levels are not obviously affected by infusions of blood saline or glucose nor are the quantitative differences in response to minor and major operations at present well demonstrated Franksson *et al* (1954) indeed suggest that the mod *of reaction seemed independent of the type or extensiveness of* the operation The persistence of the raised plasma steroid level which is *maximal within four hours of operation* varies from 24 to 72 hours and in patients developing complications high levels may persist beyond this period

The rise and duration of the raised plasma steroid levels does not bear a simple relationship to adreno-cortical output it is also dependent on the rate of conjugation by the liver the diffusion space (greater *in* the wasted) the rate of metabolic degradation and urinary excretion It is not correct to assume that *increased adrenal production* ceases when the plasma level returns to normal as this may and probably does mean that *the disposal of the steroids has caught up* with their production rate

Very little is known of the fate of steroid at the cell level it is known however, that failure or impairment of liver function will delay con jugation and thereby excretion of plasma steroids (Tyler Schmidt Eik Nes, Brown and Samuels 1954) Impaired conjugation and meta bolism of steroids may account for the high plasma levels found in dying patients (Sandberg Eik Nes Migeon and Samuels 1956) or in shock It is known that in haemorrhagic shock the fall in adrenal blood flow is compensated by an associated rise in corticoid concentration the total production therefore does not fall

Urinary Excretion of Adrenal Metabolites

The fate of administered hydrocortisone can be detected by labelling the steroid with C_{14} (Peterson Wyngaarden Guerra Brodie and Bunim 1955) In normal subjects the level of tagged plasma steroids following intravenous administration is reduced by a half in less than two hours the steroid metabolites are by then in about equal parts conjugated and free Of these steroid compounds approximately 90% is excreted in the urine and 4% in the faeces unchanged urinary hydrocortisone represents less than 1% of the administered hormone About 50 % of oral cortisone is excreted in the normal patient within four hours the main urinary metabolite being tetra hydrocortisone conjugated with glucuronic or sulphuric acids It is apparent therefore that the metabolic turnover of cortisone is rapid and large amounts of steroid can be removed in relatively small volumes of urine Jepson Jordan and Levell (1956b) found for example 46 mg of ketogenic steroid in a 500 ml specimen of urine If therefore we suppose that renal and hepatic function is adequate and that the metabolic processing of corticoids by the tissues in the post-operative phase reflects the normal pattern then the estima tion of the total corticoids excreted in the urine may give a more accurate quantitative assessment of the operative response than the plasma levels

In general the longer and more traumatizing the operation the greater the urinary steroid response although as with many other metabolic changes such as those of sodium potassium and nitrogen a wide variation in individual response is apparently compatible with an uneventful convalescence (Moore *et al* 1955) Following a major abdominal operation such as partial gastrectomy the increased excretion of urinary corticoids lasts for two to seven days In one series the mean excretion for the first four post-operative days was 26 6 mg /24 hr for a partial gastrectomy and 17 6 for an inguinal herniorraphy (Reece Edwards and Jepson 1957) The range of re sponse for patients submitted to partial gastrectomy was a wide one (15 7–45 0 mg /24 hr) and it is not possible to correlate this wide variation with other factors such as technical procedures length of operation physique or anaesthetic agents The peak excretion may occur

on any of the first three days and both its incidence and its magnitude are difficult to correlate with plasma levels (Steenburg Lennihan and Moore, 1956) Cases have been reported where a major operation was unassociated with any rise in urinary steroid excretion (Hardy, 1955) Intravenous infusions of corticotrophin produce a comparatively wide range of maximal individual response although this does not necessarily predict the response to surgery (Jepson Edwards and Reece 1956a) Post operative infusions show the adrenal gland to remain responsive to the stimulation and in the absence of gross pathological lesions in the adrenal glands it is unlikely that adrenal failure occurs

Patients with malignant disease usually have a normal excretion increased levels have been reported with massive and necrotic growths The response to operation of patients with neoplasm generally falls in the expected range for non malignant cases, although with advanced growths minor procedures may involve large and unpredictable responses The resting urinary excretion of 17 hydroxycorticoids corrected for a standard height and weight, falls a little with age (Borth, Linder and Riondel 1957) The response to operation is however, not perceptibly modified Electrolyte imbalance or depletion—as for example in patients with alkalosis pyloric stenosis and gross depletion of sodium potassium and chloride—is associated with normal excretion patterns for steroids Second operations shortly following a first result in a decreased 17 hydroxycorticosteroid excretion

The ketosteroid excretion in the urine, which is derived from corticoid degradation adrenal androgens and testosterone may or may not rise above the pre operative values (MacPhee 1953 Moore, 1954 Jepson *et al* 1956b) and little useful information has been derived from the estimation The known presence of a salt retaining factor in some human urine led to the discovery by Simpson *et al* (1952) of a new steroid aldosterone which although produced by the adrenal cortex is not affected by circulatory corticotrophin Llaurado (1955) using a bio assay has detected very greatly increased amounts of aldosterone after operation and found that the excretion levels of this corticoid correlate quantitatively with Na^+/K^+ in the urine of patients before and after operation Further work, probably with more sensitive methods of assay is needed before the importance of aldosterone in post operative electrolyte regulation can be evaluated

The Metabolic Response to Total Adrenalectomy

The evidence available to date suggests that following injury the hypophysis is stimulated to increase the circulatory corticotrophin This in turn increases the production plasma concentration and urinary excretion of co ticosteroids particularly hydrocortisone corticosterone and the ke [illegible] In addition by s[illegible]hanism as yet unknown

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It is not known however how these widespread changes are initiated controlled and terminated Many of the metabolic effects of injury can be reproduced by the administration of corticotrophin or cortisone These include the negative nitrogen balance the retention of sodium and water the urinary leak of potassium the fall in the eosinophil count and the increase of the excretion of ketosteroids and total 17 hydroxycorticosteroids The close correlation between the results of trauma and of enhanced adrenocortical activity has led to the suggestion that the first phase of accelerated catabolism after injury is due to the raised production of corticosteroids and the second phase to their withdrawal Moreover it is known that patients with adrenal hypo secretion as in Addison s disease withstand operation badly and are liable to develop profound hypotension with minimal trauma There are nevertheless difficulties in accepting this simple schema The experiments of Ingle (1952) and his associates have shown that the adrenalectomized animal maintained on a constant dose of corticos teroid responds metabolically in an essentially normal manner to trauma In the rat the presence of circulatory steroids is necessary for the development of the response but does not appear to initiate or control the biochemical changes There is some evidence that the amount of hormone required to preserve the animal is greater following injury than in the resting state Engel (1951 1953) presented evidence to suggest that overdosage of adrenocorticoids sensitized the animal to stress so that it responded by a negative nitrogen balance which other wise would not have been detectable

This experimental work which was mainly concerned with rats has now been applied to humans and their metabolic behaviour follow ing the operation of total hypophysectomy or total adrenalectomy plus oöphorectomy has been studied (Mason 1955 Graber and Beaconsfield 1955 Jepson Jordan Levell and Wilson 1956c) When such patients are maintained on a constant parenteral dose of cortisone before during and after operation the metabolic pattern induced by trauma is similar to that in the adrenal intact patient In the post operative phase sodium and water are retained potassium and nitrogen lost and the eosinophil count falls These changes are quantitatively pro-portional to the amount of trauma rather than to the maintenance dose of cortisone (Jepson *et al* 1956c) Although the pattern and apparently the range of response is similar to normal caution should be used in the interpretation of these studies It is not yet known for example what changes in plasma corticoid concentration occur during the traumatic

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and post traumatic period, even though the dose is maintained constant In addition the cortisone administration has in general been of a high dosage It would nevertheless be reasonable to suppose that a basal level of plasma corticosteroids is necessary to sustain trauma, that in order to present the familiar picture of metabolic response the body does not necessarily need a fluctuating exogenous supply of adrenocortical hormones that the known cortico steroids do not initiate or terminate the response *

The other component of the adrenal gland to consider is the medulla Von Euler and his associates have estimated the urinary excretion of catechol amines after operation (Franksson *et al* 1954) They found that in most patients with an uncomplicated convalescence the adrena line and nor adrenaline excretion was usually within normal limits during the first post operative week occasional high values of nor adrenaline were observed In association with post operative complica tions the excretion of one or both of these hormones may be greatly increased immediately following the trauma Pre operative medication the threat of operation or ether anaesthesia caused no rise in the plasma concentrations of adrenaline or nor adrenaline Operations of moderate severity were similarly ineffective although trauma in the conscious patient produced raised values, and in one case of severe burns the levels were markedly elevated before death (Hammond Aronow and Moore 1956) The accumulated evidence from the patients submitted to adrenalectomy, however excludes the adrenal medulla as an essential link in the chain of metabolic response

Histochemical Changes in Adrenal Cortex

The pathological changes in animal and human glands produced by prolonged and severe stress have been extensively investigated by Tepperman Engel and Long (1943) Selye (1946) and Uotila and Pek karinen (1951) the weight of the adrenal increases with hypertrophy of the cortical cells and a reduction of cholesterol and ascorbic acid Rich and Berthrong (1949) using the enzyme ribonuclease demonstrated that the basophilic granules contained ribonucleic acid and observed that these granules were particularly marked when death followed a severe infection Symington and Davidson (1956) further investigated adrenal

* This question continues to stimulate considerable interest and discussion It has been amply confirmed that an adrenalectomized animal supported by a constant dose of exogen ous corticosteroid undergoes many of the well recognized biochemical sequelae to tissue trauma Under these conditions the plasma corticosteroid concentration following trauma may rise though there is some difference of opinion on this point and the number of re ported observations is not large In any event the change in plasma concentration is not great Probably of more importance are the concentrations and effects of corticosteroid at the cell level but little information is at present available (See F D Moore Endocrine changes following trauma in man and subsequent discussion *Recent Progress in Hormone Research* XIII 1957 Academic Press New York)

glands obtained at operation and post mortem and suggested that ribonucleic acid and lipid phosphorus increased in the zona fasciculata after corticotrophin administration and stress This is of great interest in view of the known participation of high-energy phosphates in corticosteroid synthesis

Circulating Eosinophils A decrease in the number of eosinophils in the peripheral blood is regularly produced either by adequate stimulation of the adrenal gland with ACTH or by the administration of adrenal steroids such as cortisone or hydrocortisone It is also clearly established that a definite eosinopenia develops after injury and that thereafter the eosinophil count rises either to normal or transitorily to above normal values The changes in eosinophil concentration in the peripheral blood often but not invariably show an inverse correlation with the 17 hydroxycorticoid excretion in the urine after trauma Adrenaline causes a variable degree of eosinopenia which is maximal two to four hours after the injection after intravenous corticotrophin the eosinopenia is maximal after four hours The eosinopenia after adrenaline injection is unrelated to any rise in the plasma level of 17 hydroxycorticosteroids (Hunter Bayliss and Steinbeck 1955) Several investigators have observed in patients with Addison s disease a significant decrease of blood eosinophils following the administration of adrenaline whereas they showed no eosinopenia following ACTH These observations suggest that in man adrenaline does not cause increased adrenocortical secretion Of greater significance are the observations that in patients after bilateral adrenalectomy receiving daily 100 mg of hydrocortisone or cortisone the eosinophil count fell after operation and then subsequently rose to the pre operative level or above in spite of the continuing constant administration of the hormone (Thorn 1952 Jepson *et al* 1956c) Clearly in these cases the eosinopenia and later rebound cannot be interpreted as due to an excess and withdrawal of adrenal cortical hormone

Consid rable caution must be exercised in relating blood eosinophil levels to adrenal cortical function There is a wide physiological range in eosinophil counts and the diurnal variations in normal people are large (Swanson Bauer and Ropes 1952) The interpretation of results based on them alone is accordingly hazardous—particularly so after major surgery where so many other factors have to be taken into account

Anterior Pituitary

Adrenocorticotrophic Hormone Research in recent years has clearly shown that this secretion of the anterior pituitary gland is the most important factor in controlling adrenal cortical function (Ingle 1951) While the stimulating action of ACTH on the target gland is firmly

established relatively little is known regarding the mechanism whereby this function of the anterior pituitary is regulated The evidence in man is particularly scanty, but it is clear that this gland must play a major part in controlling the adrenal cortical activity associated with trauma Although a large amount of experimental work has been carried out in animals there is still considerable uncertainty regarding the pathways involved Specie differences may well occur and the results should be applied to man only with caution

At present the general opinion is that there are several mechanisms for the regulation of ACTH secretion (Long 1952) One is concerned with the rapid release of ACTH after injury and may be mediated in part by the nervous system An intact hypothalamus is essential (Hume and Wittenstein 1950 McCann 1953) Opinions on the role of adrenaline have been conflicting It has recently been demonstrated in man that the intravenous infusion of adrenaline increases neither the blood 17 hydroxycorticosteroids nor the urinary excretion of cortical steroid metabolites (Sandberg Nelson Palmer Samuels and Tyler 1953) Many of the earlier conclusions regarding the role of adrenaline and of the autonomic nervous system were based on indirect methods of measuring adrenocortical activity As better methods of estimating this function are developed the part played by the adrenosympathetic system in controlling the release of ACTH will become more apparent

The rate of ACTH secretion is undoubtedly under most circumstances sensitive to the level of circulating corticoids After adrenalectomy the release of ACTH is increased The administration of an excess of adrenal cortical hormones depresses the release of ACTH (Ingle 1951) The relation of this mechanism to the changes in blood levels of corticoids following severe injury is difficult to interpret The high level during stress cannot apparently be reconciled with this self regulating mechanism

Mason (1955) studied two patients undergoing total hypophysectomy for carcinomatous metastases who were maintained before and after operation on a constant dose of cortisone (60 I U daily i v) Sodium and chloride were retained while the nitrogen and potassium loss increased as would be expected in the normal patient These results indicate that certain features of the post operative metabolic response are common to the hypophysectomized adrenalectomized and normal patient This does not of course invalidate the well documented changes in corticotrophin and adrenocorticoid secretion obtained in normal patients subjected to operation it does however stress that many of the alterations are not intimately controlled by circulatory corticoids corticotrophin or indeed any of the other pituitary hor

Growth Hormone Little is known about the part if any, played by this hormone in the restitution of body composition after the catabolic phase It has however recently been demonstrated that intravenous administration of growth hormone in man accelerated the rate of dis appearance of injected amino acids from the blood (Carballeira Elrick MacKenzie and Browne 1953) The urinary amino nitrogen excretion was reduced in these growth hormone experiments As the blood non protein nitrogen levels did not increase over those observed in control experiments, the results suggest that growth hormone leads to an in creased rate of incorporation of amino acids into the tissues During the anabolic phase of convalescence lean tissue is being rapidly recon stituted with retention of nitrogen in the body Whether this process is under the control of or is influenced by growth hormone remains to be determined

Thyroid

Studies in experimental animals particularly rats have suggested that such stimuli as a cold environment violent exercise injections of formalin anorexia or spinal-cord transection may alter thyroid func- tion by depressing the rate of uptake of iodine by the thyroid and by increasing the rate of peripheral utilization of the actual thyroid hor mone (Engstrom and Markardt 1955) Adrenocorticoids depress the iodine accumulating function of the thyroid in animals without altering the rate of release of the hormone from the gland (Hill Reiss Forsham and Thorn 1950)

The evidence for functional alteration of the thyroid and its hormones in man after trauma is less secure Engstrom and Markardt (1955) followed the levels of serum precipitable iodine (SPI) in twenty four patients before and after operation and could detect no significant alteration Acute medical illness such as coronary occlusion was not usually associated with abnormal concentrations of SPI nor did parenteral cortisone suppress or augment the level

Shipley and MacIntyre (1954) estimated the effects of stress thyroid stimulating hormone and corticotrophin on the level of hormonal ^{131}I of the serum (butanol-extract) In three of the nine patients sub mitted to surgery they found a threefold increase in hormonal ^{131}I at 48 hours after operation Goldenberg Lutwak Rosenbaum and Hayes (1955) using radioactive iodine excretion and neck uptake as indices suggested that the thyroid responds immediately to stress and that its hormones may play a part in the ensuing negative nitrogen balance

On the evidence available it appears that thyroid function as esti mated by present techniques is not dramatically influenced by surgery and probably modifications in thyroid activity do not play an essential part in post operative metabolic changes

Posterior Pituitary

It has long been recognized that for the first day or two after operation little urine is formed (Pringle, Maunsell and Pringle 1905 Le Quesne and Lewis, 1953) This water retention is independent of sodium retention and in uncomplicated traumatic cases rarely lasts longer than two days The urine at this stage has a high specific gravity and electrolyte concentration Similar features are readily produced in normal subjects by the administration of antidiuretic hormone (Lloyd 1952) The normal stimulus provoking the release of antidiuretic hormone is a rise in the osmotic pressure of the plasma (Verney 1946) There is however, no evidence that this is the mechanism in post operative cases as the water retention still occurs even in overhydrated patients Pain, anaesthetics and morphine have all been regarded as factors leading to the release of antidiuretic hormone Direct measurement of the concentration of antidiuretic hormone in human plasma is difficult but clearly this information is required before the role of the posterior pituitary gland in producing the post traumatic oliguria can be finally assessed

Significance and Interpretation of the Metabolic Changes

While a considerable amount of information has been gained concerning the actual biochemical changes in body composition that develop as the result of an injury relatively little is known about the significance of these changes to the patient It seems reasonable to suppose that the convalescent process is the result of homoeostatic forces summoned by the acute injury to ensure wound healing regrowth of lost tissues and return to activity and reproduction

Immediately after receipt of an injury there are at least two important considerations—the necessity to ensure an adequate circulation for the supply of nutriment and oxygen to the vital organs and provision of sufficient energy and raw materials to restore the damaged parts Many of the biochemical changes already described may be viewed in these terms

The maintenance of extracellular fluid volume in support of plasma volume and blood pressure is clearly a vital necessity during the acute period after an injury This is served by the retention in the body of water and of sodium and chloride The maintenance of body sodium and chloride with an adequate store of water is essential to the refilling of plasma volume after haemorrhage It is important to emphasize that under natural conditions or in the absence of transfusion this mechanism is the only one available for immediate restoration of blood volume

The interpretation of the changes observed in the plasma concentrations of electrolytes after trauma presents many difficulties which have

not yet been resolved The fall in the concentration of sodium and chloride is not due to an external loss of these substances On the contrary at this stage they are being avidly retained within the body and the fall still occurs even if additional sodium chloride is given At the same time a rapid catabolism of lean tissue and fat is occurring There is thus a loss of potassium and other electrolytes from within the cells and the production of water from the burning of fat Retention of water may lead to dilution of the extracellular fluid but the decreases of serum concentrations have been observed in cases in which no excess of water has been given and no measurable rise in total body water has occurred The decrease may be aggravated by giving an excess of water in the immediate post traumatic period The extracellular fluid volume may be increased after injury even if there is no addition from external sources (Blixenkrone Møller 1949 Wilkinson Billing Nagy and Stewart 1950) The source of the fluid is presumably from cells and fat metabolism There is some evidence that such an internal dilution of the extracellular fluid may take place as there is usually also a fall in plasma protein concentration though this change must be interpreted with caution as rapid catabolism of protein is occurring at the same time While a shift and retention of water may be the whole explanation of the changes in plasma sodium and chloride concentrations direct evidence is lacking owing to the difficulty of accurate definition and measurement of a compartment where fluid is held in the body outside cells Another possible explanation is that sodium and chloride leave the extracellular fluid and enter the cells bones or gastro intestinal tract Here again direct evidence is lacking but it should be noted that the bones contain much sodium but little chloride The sodium in human bone may possibly act as a metabolic reservoir but no such store of chloride is known

Occasionally after surgery a more persistent decrease in the concentration of serum electrolytes is seen This usually occurs in debilitated patients and is analogous to the hyponatraemia seen in many chronic wasting diseases The serum concentrations are not restored to normal by either fluid restriction or salt administration and the condition is generally corrected only by an improvement in the nutritional state Other causes of persistent hyponatraemia after surgery are unrestored salt loss or overloading with water in a patient with impaired renal function (Wynn 1956)

The rapid catabolism of fat and lean tissue probably has as its primary purpose the provision of energy and raw materials for the healing of the wound The metabolic mobilization of nitrogen and of the intracellular electrolytes provides the substances essential to the synthesis of new protoplasm This concept introduced by J S L Browne (1950) of the loosening of body nitrogen to make it available

for wound healing is of great interest The evidence that the intra cellular changes of the first phase have as their purpose the provision of substances for the formation of new tissue in the wound outweighs the opposite contention that this catabolism is a deleterious effect It is significant that the healthy person who heals his wound well after a single trauma and thrives clinically shows this catabolism most vigorously and the depleted person who is much more apt to fail in healing (wound dehiscence non union of fractures) does not show a vigorous catabolism

One may inquire why so much tissue is catabolized to heal a small wound (Moore 1953) In a simple abdominal laparotomy the transverse healing of the incised wound and of any intraperitoneal manipulations probably does not entail the formation of much more than 20–50 g of tissue at the most In all likelihood the actual weight of new tissue formed is even smaller than this Yet this must occur in the presence of a re duced diet, and nature makes available an abundance of the necessities Between 1–2 Kg of tissue may be destroyed to form this small amount of crucial new tissue in the wound For a large war wound a femoral fracture or a burn an even greater mobilization of nitrogen occurs The supply of amino acids polypeptides and intracellular electrolytes is continuously increased and made available to the wound *Many of* these substances are toxic in the extracellular phase if their concentra tion is increased and accordingly there is of necessity a continuous increase in their excretion in the urine As the immediate threat to life recedes there is a gradual transition from emergency to trophic mechan isms Fibrosis begins in the wound and its tensile strength rapidly increases Reopened at three days a wound readily falls apart After six days it has to be cut That this can and frequently does occur in the absence of diet is a tribute to the effectiveness of cellular mobilization in the catabolic phase and to the rapidity of fibrosis and collagen deposition once rapid catabolism ceases

In phase III as dietary intake increases the tissues depleted in phase I are gradually restored and muscular strength is slowly regained Wound changes are still occurring consisting of collagen deposition consolidation of the scar and increase of tensile strength The wound and muscle clearly occupy top priority in this phase of regrowth

In phase IV the wound drops to lowest priority as activity in it ceases Muscular strength has been restored and finally only the body fat consumed during the early stage has to be replenished Once this has been done convalescence is complete Prior to this time should the patient suffer a second injury he will show the modified response observed in depleted subjects After the fat gain phase he will show the complete picture of the normal metabolic response

Therapeutic Considerations

A detailed account of the post-operative care of surgical patients from the metabolic point of view is not within the province of this article but has been fully described elsewhere (Moore and Ball 1952) Certain general principles may however be deduced from a considera tion of the biological processes occurring after an injury

The prompt restoration of blood lost by haemorrhage is of first importance This was clearly shown by the experience gained in the treatment of war wounds (Grant and Reeve 1951) and has been con firmed by many later investigations Furthermore the plasma proteins given by transfusion are retained in the vascular compartment and are not immediately available for catabolism and excretion

It has already been noted that the most vigorous catabolism after trauma is observed in healthy well nourished individuals This cata bolism of fat and lean tissue is a physiological process which cannot be checked either by forced feeding of protein or by the administration of hormones promoting anabolism The capacity to respond to injury with increased breakdown of protein is an asset to the organism though it does not necessarily follow that wound healing will be more rapid as many other factors affect convalescence and final recovery However it has long been recognized that debilitated and undernourished patients are poor operative risks Thus whenever possible the protein stores of the body should be filled before an operation is carried out Im mediately after operation the patient has little appetite and forced feeding at this stage is of no benefit and merely adds to his discomfort On the other hand as soon as the catabolic phase is over—often about three to five days depending on the nature and severity of the trauma—nitrogen is readily retained and the intake should be rapidly increased At this stage every effort to provide calories must be made A calorie gram of nitrogen ratio of 100 or over is desirable If intake by mouth is inadequate the intravenous route must be used In patients depleted by previous illness the catabolic phase is brief If the underlying condition has been relieved high intakes in the early post operative period are utilized sooner and better by them than by their well nourished counterparts The crucial question to determine in an ill or complicated patient more than five days after an injury is whether he is coming into positive balance—he cannot convalesce otherwise The weight curve may give some indication but there is no simple short cut to the determination of nitrogen balance The intake may be approximately calculated from ordinary tables and measured portions The chemical measurement of the total (24 hour) nitrogen excretion in the urine is neither difficult nor time consuming with the Kjeldahl digestion distillation apparatus It should be made available whenever difficult problems are being managed

Similar considerations apply to potassium metabolism Any potassium deficiency existing pre operatively must be corrected The large potassium loss which develops immediately after operation is a physiological process *which cannot* be checked by the provision of excess potassium After the third day this increased excretion ceases and restoration of the loss is begun At this stage increasing dietary intake usually provides sufficient potassium If however intake by mouth cannot be resumed intravenous potassium should be given with glucose

After injury there is a retention of sodium chloride and water and any excess given at this stage *is held in the body The patient may* thus readily be overloaded The fall in serum sodium concentration which occurs after operation does not indicate a deficiency of sodium in the body The indication for additional sodium or chloride is the demonstration of an abnormal loss from the body such as by exudates from wounds *or by vomiting It is perhaps a misfortune that the concentration of* sodium in the serum is now so readily measured by flame photometry A more valuable use of this instrument in therapeutics is the determination of the sodium concentration in these extrarenal losses so that accurate replacement may be carried out

Routine weighing of patients can yield information of the greatest value and it is important that a suitable scale should be available Physiologically there is a loss of weight after injury due to the catabolism of lean tissue and fat A gain or maintenance of weight after a major operation is an indication of water retention

The practical guide to the care of a patient after an injury of any nature may best be described as thinking in terms of balance During *the first two phases the patient requires no more fluid* and electrolyte than what he has lost During the later phases adequate diet must be provided to restore his body composition to normal with regard to lean tissue and fat

Conclusion

The metabolic changes that occur after an injury represent a fundamental biological process designed to ensure survival of the individual and healing of the damaged structures Though the features are most readily studied after a definitive surgical operation there is little doubt that a similar train of events takes place *after any type of injury* whether by direct trauma by infection, ischaemia or any other destructive process Appropriate specific measures dealing with the causal agent and the local disturbance constitute one aspect of therapeutic care The other aspect concerns the patient as a whole and his general reaction to the noxious agent—an aspect *frequently overlooked* in these days of rapid development of specific remedies Yet it is of fundamental

importance in the everyday care of patients and worthy of the most detailed study

It is apparent that during the past few years a large amount of information has been obtained on the metabolic aspects of the recovery from injury This has greatly helped clinicians to deal more logically and perhaps more successfully with metabolic problems developing in their patients The gaps in our knowledge are still large and much more information is required particularly about the changes occurring within the cells and enzyme systems The mechanisms by which the metabolic response is triggered controlled and ended are unknown The physico-chemical changes in the wound itself have been little studied and therein may be the key to many of the unanswered questions

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CHAPTER 5

METABOLIC ASPECTS OF LIVER DISEASE

A L LATNER

ALTHOUGH work is proceeding at an increasingly rapid rate on numerous metabolic aspects of the normal and diseased liver it is proposed in this chapter to deal only with those findings that have clinical significance at the present time It is in no way intended to decry many excellent publications dealing with liver enzymes phosphate turnover mitochondrial metabolism and the like Such investigations will no doubt eventually contribute much of great value to the clinician and it must be left to some future author to put them in their rightful place

To the practising physician and surgeon studies of hepatic metabolism are chiefly of importance in so far as they shed light on the aetiology of certain common liver diseases elucidate the production of symptoms and signs lend aid in diagnosis and point the way to rational therapy It is with these considerations in mind that the subject matter of this chapter has been compiled

Aetiology of Liver Disease

During the last few decades much effort has been spent on the nutritional aspects of liver disease and has led to the brilliant studies of Himsworth and his colleagues Certain nutritional mechanisms have been recognized as causative factors in the production of diffuse hepatic fibrosis by way of a preceding fatty infiltration whilst others have been related causally to acute necrosis and post necrotic scarring

Fatty Liver and Cirrhosis

Since Minkowski (1893) first produced diabetes in dogs by the removal of the pancreas it has been known that this operation is followed by fatty infiltration of the liver The infiltration is of two types In the depancreatized animal deprived of insulin the accumulation of fat in the liver is related to the fact that carbohydrate is not readily available as a source of energy The mechanism is precisely that which occurs in starvation and is accompanied by ketosis and hyperlipaemia The latter is due to the rapid mobilization of fat from the depots as a source of energy The fat accumulates in the liver and then undergoes metabolic breakdown This gives rise to ketone bodies at a rate greater than can

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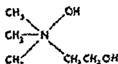
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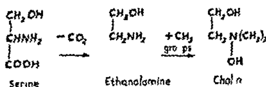
be dealt with by the tissues and so results in ketosis This type of fatty liver is often referred to as the physiological fatty liver There is no real disturbance of liver function and so, in spite of the hyperlipaemia there is no profound disturbance in other lipids of the plasma and the phosphatide and sterol patterns remain normal

On the other hand administration of insulin to depancreatized dogs does not indefinitely prolong life Allan Bowie Macleod and Robinson (1924) first demonstrated that such animals eventually developed symptoms suggestive of hepatic dysfunction *Post mortem* examinations revealed intense fatty infiltration of the liver This sequence of events could be prevented by adding raw pancreas to the diet Some years later Hershey (1930) found that egg yolk lecithin could replace raw pancreas and subsequently Best Ferguson and Hershey (1933) demonstrated that choline was the active constituent of the lecithin Choline has the formula



It is particularly rich in methyl (CH_3—) groups and can donate them to other substances during metabolism by means of the process known as transmethylation It will for example react with guanidoacetic acid to form methyl guanidoacetic acid better known as creatine In fact it is possible by feeding large amounts of the former substance to rats so to exhaust the availability of methyl groups as to produce a conditioned deficiency of choline and give rise to an intense fatty infiltration of the liver Alternatively the infiltration can actually be produced by feeding diets deficient in choline

Choline itself arises in the body by the methylation of ethanolamine which is in turn derived from the amino acid serine The sequence of events is as follows



It might therefore be e[illegible] any [illegible] choline
donating methyl groups [illegible] the fe[illegible] of its
deficiency fatty liver by [illegible] body to [illegible]
own choline It is not s[illegible] are
(1935) [illegible] that [illegible] of [illegible] sein

was effective from this point of view for casein contains the amino acid methionine which possesses a labile methyl group

Substances like choline and methionine which prevent this type of fatty liver are said to be lipotropic It must be emphasized that we are now dealing with the pathological fatty liver There is actual diminution of liver function with marked disturbances in the lipids of the blood in contrast to the physiological fatty liver already mentioned

So far we have been considering fatty livers as they occur in animals There is however ample evidence that a similar condition occurs in man Its association with diabetes mellitus is well recognized It has long been known in association with malnutrition Trowell (1949) has described the so called malignant malnutrition of infants in Africa (Kwashiorkor) in which a fatty liver is a prominent feature It was also relatively common in recent famines in Europe resulting from the Second World War *By means of serial liver biopsy it has been possible* to demonstrate that the excess of fat will disappear as a result of feeding high protein diets methionine or choline

If animals are kept on a choline deficient diet for long periods of time *the histological picture of the liver gradually changes diffuse* fibrosis appears and a condition indistinguishable from so-called Laennec s cirrhosis is produced

Evidence from Human Sources Rokitansky (1849) first suggested that a similar mechanism was possibly involved in the production of the human condition This was amply demonstrated by Connor (1938 and 1939) who in a group of post mortem examinations of known alcoholics demonstrated all stages of gradation from the fatty liver to cirrhosis The alcohol itself is probably not the direct cause of the lesion The continuous expenditure of the alcoholic on his craving not only gives him a gastritis which impairs his appetite but also deprives him of sufficient money to enable him to buy adequate amounts of the relatively expensive high protein and lipotropic foodstuffs

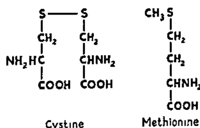
Gillman and Gillman (1945) have demonstrated by means of liver biopsy similar changes in malnourished African children and a number of other papers have appeared in the literature which fully confirm this transformation

The *transition from a fatty liver to a diffuse cirrhosis is probably* a particular example of a general principle in which chronic infiltration of any kind occurring in the liver eventually results in fibrosis Pathological changes of this type can occur in glycogen storage disease as well as in the lipoidoses

Hepatic Necrosis

It has been known for many years that the diet markedly affects liver injury produced by poisons Weichselbaum (1935) however was the

first to show that such injury could be produced by dietetic deficiency alone He showed that rats fed a diet low in casein became ill and died Lesions which he described as haemorrhages could be demonstrated in the liver They were prevented by giving the amino acids cystine or methionine, the chemical structures of which are shown below It will be noted that both contain sulphur



Gyorgy and Goldblatt (1939) first showed that the haemorrhagic lesions were really areas of acute necrosis It was assumed however by most workers that these lesions were just a stage in a pathological sequence leading to so called cirrhosis There was at this time much confusion in relation to the experimental production of cirrhosis of the liver Daft Sebrell and Lillie (1942) suggested that the necrosis and the fibrosis were two different conditions This was based on experimental evidence which showed that various dietary supplements affected differently the incidence of these two types of lesion It was left however for Himsworth and Glynn (1944) to produce each type independently of the other As already discussed, diffuse hepatic fibrosis was produced as a result of diets giving rise to prolonged fatty infiltration of the liver Massive necrosis however resulted from diets deficient in protein This could be achieved by feeding only small amounts of casein In one species of rat if the intake was dropped to 200 mg massive necrosis soon developed A daily ration containing 500 mg of this protein maintained good health On the other hand when yeast protein was used in place of casein relatively large amounts did not prevent the onset of massive necrosis Yeast protein is deficient in methionine The lesion could be entirely prevented if about 20 mg of this amino acid were given daily as a supplement Hock and Fink (1943) had also been working along similar lines, but they showed that the yeast necrosis could be prevented by administration of cystine Since this latter substance can easily be derived from methionine in the body, it was not clear which of the two amino acids was active in preventing necrosis The problem was solved by feeding diets containing mixtures of synthetic amino acids in place of protein (Glynn Himsworth and Neuberger 1945) When ample cystine was present methionine deficiency did not produce necrosis but resulted in the production of a macrocytic

anaemia and hypoproteinaemia It was possible to determine how much methionine could just prevent these abnormalities When this amount was given in a diet from which cystine was omitted massive necrosis of the liver was produced This latter amino acid must therefore have been the nutritional factor the absence of which gave rise to the liver lesion

Although this evidence seemed very clear other workers could not reproduce the results or obtained them somewhat inconstantly Gyorgy (1947) in America demonstrated that the incidence of necrosis seemed to bear some relationship to the type of fat administered at the same time as the protein-deficient diet He showed that it was the tocopherol content of the fat that was important in this respect The incidence of massive hepatic necrosis in animals on a diet deficient in sulphur containing amino acids was markedly decreased when ample amounts of this vitamin were administered Himsworth and Glynn had in advertently omitted this substance from their experimental diets In actual fact their diet was deficient in both cystine and tocopherol Other workers in attempting to produce a pure cystine deficiency had added all the known vitamins including tocopherol It must be em phasized however that adequate supplies of cystine will prevent the lesion even though tocopherol is not administered Unknown to English and American workers Schwarz (1944) in Germany had also demon strated the preventive action of the vitamin Himsworth and his col leagues have adequately confirmed this finding and have also shown that the facility with which liver necrosis can be produced depends on the previous dietary intake of tocopherol If this is low the lesion is produced much more readily

Schwarz has shown that another food factor is necessary for the pre vention of necrosis He has called it Factor 3 It is present in certain yeast extracts and in impure casein Its chemical nature has not yet been determined

Other factors are also concerned young growing rats seem to be more susceptible and males more so than females Environmental tem perature and time of weaning are also of importance (Naftalin 1954) The digestibility of the diet must also be considered for example diets in which crude soya bean meal is given as the source of protein should contain adequate amounts of cystine Nevertheless such diets readily lead to liver necrosis If however the meal is heated before administra tion the lesion does not develop Soya bean meal contains a trypsin *inhibitor* which is inactivated by heat This substance interferes with pancreatic digestion and consequently with the liberation of amino acids in the intestine Heating destroys its activity and the sulphur containing amino acids of the diet can then be released and assimilated

The left lobe of the liver is more liable to develop necrosis than the right Himsworth and Glynn (1944) explain this in terms of the circula

tion The right lobe receives all the blood from the small intestines and consequently has direct access to such protective amino acids as may be available There is, however, another explanation The left lobe is more directly exposed to toxic material arising in the gut by bacterial action since this is much more likely to be absorbed from the large bowel the venous drainage of which passes to the left half of the liver Because sulphathiazole has no preventive effect on rats receiving a necrogenic diet Himsworth has suggested it is unlikely that bacterial toxins play any significant part in the production of the lesion More recently however Gyorgy and Stokes (1951) have shown that aureomycin markedly delays the onset of necrosis in rats fed the yeast diet of Himsworth and

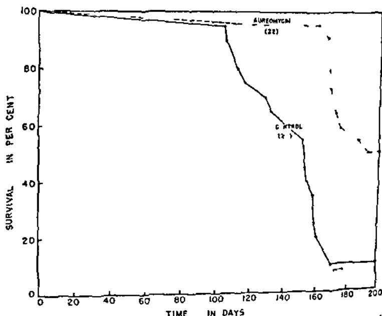


FIG 1 Survival of controls and aureomycin treated rats on yeast diet producing liver necrosis (Gyorgy P and Stokes J Jr in Ciba Foundation Symposium on Liver Disease Churchill)

Glynn (see Fig 1) Terramycin and streptomycin have a similar effect but other antibiotics including penicillin are ineffective The effective substances are so vastly different from the point of view of chemical structure that it is unlikely that their action is wholly metabolic and similar to the action of tocopherol It is probably due at least in part to suppression of the intestinal flora and the prevention of their toxic metabolites from reaching the liver

Sequelae

A number of animals survive their attack of acute necrosis The necrotic cells are replaced by fibrous tissue resulting in a coarse fibrosis

associated with areas of liver in which normal lobulation is preserved This lesion differs from the diffuse hepatic fibrosis already discussed It is the so-called post necrotic scarring of the liver The recognition of these two types of hepatic fibrosis has done much to clarify our ideas on the experimental production of cirrhosis Unfortunately however the distinction is not quite so clear in man although the same broad differentiation may be recognized

Human Necrosis and its Sequelae

Evidence is also available from human sources which relates hepatic necrosis and its sequelae to diet The so-called toxic jaundice of the tropics often confused with infective hepatitis is common among the poorer natives in countries where malnutrition is prevalent In these countries among the poorer classes tropical cirrhosis is also prevalent a portion of this is undoubtedly post necrotic scarring The lesion is identical with that following experimentally produced hepatic necrosis On the other hand children belonging to the higher castes of vegetarian Hindus are liable to develop a subacute hepatic necrosis during the first three years of life It is perhaps significant that the onset of the illness occurs shortly after weaning At this stage its victims have passed from a high protein milk diet to the relatively low protein vegetarian diet prescribed by their religion

Other Causes of Hepatic Cirrhosis and Necrosis

It would perhaps be unwise to create the impression that all liver necrosis or cirrhosis is related directly to the metabolism of the thio aminoacids or choline It seems fairly certain that a diffuse cirrhosis can develop in the human without an antecedent fatty infiltration In fact such a lesion may manifest itself after ordinary infective hepatitis especially the cholangiolitic type Hill and his colleagues in Jamaica have also demonstrated that malnutrition associated with the ingestion of some toxic agent may give rise to so-called veno occlusive disease of the liver and that organization of the intrahepatic exudate may lead to cirrhosis (Hill Rhodes Stafford and Aub 1953)

Cirrhosis may also be associated with disturbances of either iron or copper metabolism as in haemochromatosis and hepato lenticular degeneration respectively (See Chapters 12 and 13)

Various types of necrosis can occur with such different diseases as typhoid fever rheumatoid arthritis various virus diseases and even uraemia Although these diseases may possibly affect thioaminoacid metabolism it is difficult to believe that so varied a group of disorders should each give rise to a common metabolic disturbance in the liver

Poisons and Necrosis

The liver cell is susceptible to poisons derived from a large number of sources After administration to animals under experimental conditions the effects of many of them have been studied Himsworth has pointed out that these are of two broad types viz immediate experimental hepatic necrosis and 'delayed experimental hepatic necrosis The former occurs a few hours after administration of the poison but the latter may be delayed for weeks

The immediate form is produced by chlorinated hydrocarbons tannic acid, phosphorus and allyl formate by the injection of *Proteus vulgaris* endotoxin or by feeding poisonous mushrooms This type of reaction is usually zonal in distribution Unlike massive necrosis which affects the whole of the liver lobule the lesion occurs in some specific region of that structure It may be centrilobular as after carbon tetrachloride, chloroform tannic acid or mushroom poisoning On the other hand, it may be periportal as after allyl formate phosphorus or the endotoxin of *Proteus vulgaris*

Himsworth has put forward a very attractive explanation for the production of centrilobular necrosis The poison causes all the liver cells to swell In this way the intralobular sinusoids are at least partially obstructed The cells most likely to be adversely affected by this impairment of circulation are those at the centre of the lobule, which have access only to the already impaired supply of oxygen and other nutriment derived from the blood stream after the peripheral cells have absorbed their own nourishment A similar mechanism probably accounts for the centrilobular distribution of necrosis in viral hepatitis

The delayed form of necrosis so readily produced in man by cinchophen or trinitrotoluene is difficult to produce in the laboratory These compounds do not produce significant liver damage in normal experimental animals A very similar lesion can however, be produced in them by feeding grain derived from seleniferous soil This delayed type of necrosis closely resembles dietetic massive necrosis There seems little doubt that the substances involved act by producing a conditioned deficiency of cystine The lesions are prevented by supplements of casein methionine or cystine Trinitrotoluene will produce typical delayed necrosis in animals receiving low protein high fat diets although as already mentioned it has no effect when a normal diet is administered

Himsworth has suggested the adjectives toxipathic for those liver necroses due to noxious agents and trophopathic for those due to deprivation of a factor essential to cellular life be it oxygen or a nutriment There are obviously mixed types In centrilobular necrosis the toxipathic swelling of the peripheral lobular cells has led to the trophopathic necrosis of those at the centre of the lobule

Alcohol and Liver Disease

Alcohol has long been regarded as a likely causative agent of liver disease It has been shown to increase the severity of the cirrhosis pro duced in choline deficient rats This effect can however also be produced by adding sugar instead of alcohol to the diet in an amount containing an equivalent number of calories (Best Hartroft Lucas and Ridout 1949) Increasing the calorific value of the diet therefore increases the amount of choline required to maintain a normal liver In the case of the human being unfortunately the money spent on alcohol makes it difficult for the alcoholic to buy additional choline containing foods

Patients recovering from hepatic failure have been given 9 oz of 40% alcohol daily along with an ample diet supplemented with vitamin B complex They continued to make steady recovery (Patek and Post 1941)

Malignant Tumours of the Liver

Choline deficient diets have given rise to malignant hepatic tumours in a variety of animals including rats chickens and mice There may even be metastases in the lungs It is interesting to note that riboflavin administration will prevent the production of the primary tumours (Schaefer Copeland Salmon and Hale 1950)

This vitamin will also inhibit the development of malignant hepatic tumours produced by the administration of certain azo dyes (Miller and Miller 1953)

Disturbed Metabolism in Relation to certain Symptoms and Signs

Although some of the symptoms and signs of liver disease are un doubtedly of metabolic origin we by no means possess complete under standing of their mode of causation The ensuing account is intended to indicate the present state of our knowledge of these phenomena

Jaundice

As a result of continued hyperbilirubinaemia above 1 6 mg /100 ml serum bilirubin is bound in the tissues possibly to elastin In the serum all the pigment is bound to albumin It must therefore be carried to the tissues along with albumin which is now known to enter the tissue fluids quite readily a phenomenon which has been amply proved with tracer techniques In contact with the tissues in the presence of hyper bilirubinaemia, the bile pigment leaves the albumin and becomes bound to some tissue protein It seems to have a special affinity for elastic tissue It is not at all unlikely that such a continuous interchange of bilirubin occurs normally It may account for the small quantity of bile

pigment found in normal urine This must enter by some tubular excretion mechanism, since insufficient albumin passes the glomerular membranes and then remains in the urine to account for any bile pigment Exactly the same problem arises in any biluria it is extremely unlikely that bilirubin occurs in the glomerular filtrate in sufficient amount to account for the eventual deep staining of the urine found in jaundice which is not haemolytic It is well known that in the presence of intense jaundice there is little or no discoloration of the cerebro spinal fluid since only small amounts of albumin are present for carrying the pigment across the blood brain barrier It is interesting to note that bilirubin injected intravenously does not appear in the urine It does appear however, if bile salts are injected at the same time Recent information relating to the structure of direct and indirect bilirubin (vide infra) may cause us to modify our ideas of the urinary excretion mechanism

Recent biochemical research has led to much dissatisfaction with the older theories of production of jaundice This has been increased by the realization of the fact that not all the bile pigment necessarily arises from haemoglobin breakdown The latter is well discussed in a recent monograph (Gray 1953 Chapter IX) It is also now being realized that the lymphatic system of the liver is concerned in the mechanism of jaundice production A recent classification of jaundice is as follows (With 1951)

1 Production jaundice— due to hyperproduction of bilirubin
2 Retention jaundice— due to decreased excretory capacity of the liver
3 Lymphogenous jaundice—diversion of bile from the biliary system to the lymph

Much of the last named is due to so called regurgitational lymphogenous jaundice in which the bile is regurgitated into the lymph spaces through minute ruptures in the bile canaliculi caused by increased pressure as in occlusion jaundice or by necrosis of liver cells as in parenchymatous jaundice It is however obvious that most forms of clinical jaundice are mixtures of two or more of these types for example both retention and lymphogenous jaundice occur in extrahepatic obstruction and in hepato cellular disease Some forms of haemolytic jaundice are probably pure production jaundice It is also possible that the production of abnormal amounts of bilirubin by synthesis may occur in non haemolytic hereditary jaundice A similar hyperbilirubinaemia is found in the horse

According to Lemberg and Legge (1949) the bile pigment first formed from haemoglobin breakdown is the green biliverdin which

is then converted to the orange yellow bilirubin The former bile pigment does not react with the diazo reagent of the van den Bergh reaction It is thought to be responsible for the greenish tinge sometimes seen in jaundiced patients which some believe occurs more commonly in long standing obstruction of the bile duct It can of course also occur in association with hepato cellular disease

Recently Cole and Lathe (1953) have managed to separate serum bilirubin into two components by using a chromatographic technique with a silicone treated kieselguhr column One is soluble in water and gives the direct van den Bergh reaction The other is more soluble in *organic solvents and gives the indirect reaction It should be noted that* no protein is present with either type It is not therefore responsible for the difference in behaviour of various sera with the diazo reagent The indirectly reacting component is bilirubin itself The directly reacting substance which is produced in the liver and excreted in the bile is bilirubin diglucuronide That which occurs in the serum in hepatitis and biliary obstruction is probably the monoglucuronide The glucuronides are more soluble in water than bilirubin itself and would thus appear in the urine more readily

Much evidence is also accumulating with regard to the origin of bilirubin This is probably derived from three sources

1 Haemoglobin liberated from erythrocytes at the end of their life span
2 Haemoglobin or possibly porphyrin liberated from immature erythrocytes
3 Porphyrins and haems other than haemoglobin e g cytochrome and myohaemoglobin

Bile pigment in the intestine is converted into stercobilinogen some of which is absorbed into the blood and some of which becomes oxidized to the faecal pigment stercobilin The absorbed moiety passes to the liver where most of it is probably destroyed Some however is excreted into the bile and some passes through the liver and after excretion by the kidney appears in the urine as urobilinogen Urobilin is identical with stercobilin There are therefore increased quantities in the urine when there is increased production of stercobilin as in haemolysis or when there is diminished destruction and excretion by the liver as in hepato cellular disease If however no bile pigment reaches the intestine then no urobilinogen appears in the urine This occurs in obstructive jaundice Even in this case however in the presence of infection of the biliary system urobilin may be produced within these ducts It is then absorbed into the blood stream and subsequently appears in the urine

Pruritus

In general this seems to be related to the degree and duration of biliary obstruction It must be remembered however that the obstruction may be caused by swollen liver cells occluding the bile canaliculi and is not by any means solely extrahepatic There seems to be no correlation between intensity of pruritus and the levels of serum bilirubin or bile salts Administration of bile salts by mouth or injection to jaundiced patients does not increase this symptom It is suggested that the altered serum cholinesterase in liver disease may reflect a general upset of this enzyme so intimately related to the nervous system which might account for the itching It is even suggested that it is the sympathetic nervous system which is chiefly affected An interesting observation is the fact that severe pruritus in liver disease is not infrequently relieved by the injection of dihydroergotamine On the other hand this drug may act by affecting the peripheral blood flow, an increase in which seems to aggravate the itching Others have suggested that histamine is the causative agent and good results in therapy have been claimed with antihistamine drugs

Muscular Weakness

Various explanations have been suggested for this symptom so prominent in hepato cellular disease The disturbance in cholinesterase metabolism may produce some effect at the motor end plates Bile salts are known to affect these structures On the other hand disturbances in carbohydrate metabolism might explain muscular weakness There is also a fairly profound upset of electrolyte metabolism because there is a tendency for both the serum sodium and potassium levels to be lower than normal a state of affairs which in itself is often associated with asthenia Conditioned deficiency of the fat soluble vitamins due to inefficient absorption of fat from the intestine may also play some part

Haemorrhages

These are usually associated with a demonstrably low level of plasma prothrombin This is especially the case in obstructive jaundice in which condition nowadays there will usually be good vitamin K therapy Sometimes in severe hepato cellular disease, there may be bleeding without hypoprothrombinaemia For some reason administration of the vitamin occasionally checks this type of bleeding also Sometimes haemorrhage is due to a low fibrinogen content of the blood Much of it is probably due to actual damage of the capillary walls possibly of toxic origin

Coma

The ultimate cause of this disturbing symptom is obviously bio chemical in nature It has been suggested that an important factor is hypoglycaemia resulting from interference with carbohydrate metabol ism It is however by no means uncommon to find the blood sugar normal even in the relatively late stages of hepatic coma Others have blamed disordered function of the central nervous system secondary to disturbances in the metabolism of cholinesterase The writer feels that disturbances in electrolyte metabolism possibly play some part Re cently Walshe (1953) has associated the coma with the toxic effect of ammonia accumulating in the blood raised levels have in fact been

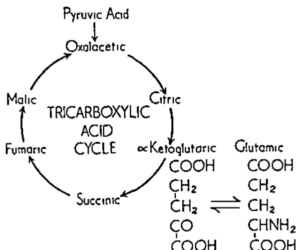


FIG 2 The incorporation of glutamic acid into the tricarboxylic acid cycle In the tissues the acids are actually in the form of their radicles

demonstrated but they are by no means invariable Glutamic acid norm ally binds the ammonia resulting from protein metabolism and becomes converted to glutamine Walshe has claimed successful treatment of coma occurring in hepatic cirrhosis by the intravenous administration of sodium glutamate Such success would seem to point to the correctness of the supposition that ammonia is the cause of the coma which is also in some way probably concerned with disturbances in carbohydrate metabolism It is well known that glutamic acid can enter the tricar boxylic acid cycle by becoming converted to ketoglutaric acid (Fig 2) It is difficult however to reconcile these views with the fact that in hepatic coma glutamic acid is usually present in increased amount in the blood

Impending or even deep coma has been reported in patients with

cirrhosis after the administration of ammonium salts ammonium ex change resins protein and urea (Phillips Schwartz Gabuzda and David son 1952) Blood ammonia concentrations rose in most but not all of these patients A similar rise has been demonstrated in patients with hepatic coma and other neurological manifestations arising directly as a result of the liver disease (Phear Sherlock and Summerskill 1955) High blood ammonia levels could be related to impaired hepato cellular function and a portal venous collateral circulation Although the blood ammonia levels were usually correlated with the severity of the neurological disturbance normal values were obtained in 10 per cent of cases It may well be that the raised ammonia level is a parallel phenomenon and not related causatively to hepatic coma

It has been shown recently that methionine given by mouth produces neurological deterioration in patients who have previously had episodes of impending coma (Phear Ruebner Sherlock and Summerskill 1956) The effect is probably due to some unknown toxic substance produced from methionine by intestinal bacteria since no toxic disturbances develop if aureomycin is given at the same time This observation may help to justify the clinical impression that administration of the anti biotic is of benefit in the therapy of hepatic coma Recently it has been shown that neomycin is probably the antibiotic of choice In doses of 8–12 g daily it can produce clinical improvement in two to four days and blood ammonia levels fall to normal (Fisher and Faloon 1957)

It is possible that the mechanism of production of the other neuro logical complications of liver disease is the same as that of coma the difference being largely one of degree

Foetor Hepaticus

Patients with severe liver disease especially those in coma emit a characteristic rather sickly odour It is likened by some to the smell of autolysed liver in the post mortem room The substance responsible for the odour is now believed to be a methyl mercaptan

Ascites

There is no doubt that many factors play a part in the production of this distressing condition These include portal hypertension hypo albuminaemia antidiuretic hormone electrolyte disturbances involving retention of sodium altered condition of the capillary walls and pos sibly lymphatic obstruction with overflow into the abdominal cavity

In relation to portal hypertension it should be realized that extra hepatic block of the portal vein does not ordinarily produce ascites Raised pressure in the portal system frequently occurs in cirrhosis un accompanied by ascites In one series of cases of cirrhosis those patients without ascites had portal pressures as high or higher than those who

had ascites (Pattison 1949) Ascites can also be produced experimentally in the dog by constriction of the thoracic inferior vena cava by a Cellophane band causing engorgement of the liver Fluid formation can occur even though the portal pressure does not rise above normal The ascitic fluid is very rich in protein Liver lymph has a high protein content and it is possible to demonstrate engorged subcapsular lymphatics after experimental production of this type of venous congestion It is suggested that the lymph overflows into the abdominal cavity

On the other hand by constricting the abdominal inferior vena cava and the portal vein it is possible to induce a chronic portal hypertension in dogs Such animals do not develop ascites If however they are rendered hypoproteinaemic by plasmaphoresis ascites will develop and the fluid is low in protein This state of affairs can be paralleled in the human being Not infrequently cases with marked portal hypertension develop ascites only after they have been rendered hypoproteinaemic by a severe haematemesis or melaena

The combination of hypoproteinaemia and portal hypertension seems to be the dominant cause of ascites in young patients suffering from a post necrotic type of cirrhosis Such patients will often respond well to the administration of intravenous albumin The middle aged alcoholic with ascites however presents a much more complicated aetiology In addition to portal hypertension and hypo albuminaemia electrolyte disturbances antidiuretic hormone and other factors play a part Such a patient as a rule does not respond well to the intravenous administration of albumin

In the post necrotic type hypo albuminaemia does not give rise to ascites solely by osmotic mechanisms In fact it is now known that intravenously administered albumin passes rapidly into the ascitic and oedema fluids The concept of a vascular wall impermeable to albumin is no longer tenable In some way not fully understood a low level of serum albumin seems to cause sodium retention by the kidney This tends to produce an over all retention of fluid in the tissues with generalized oedema The fact that ascites is often the only clinical manifestation of this state of affairs is due to the portal hypertension and the poor state of nutrition of the portal capillaries The sodium retention however is often accompanied by a low level of serum sodium These effects are almost certainly mediated through the adrenal

Spider Naevi and Palmar Erythema

According to Bean (1945) these lesions may be due to an excess of circulating oestrogens or similar hormones It seems however that the erythema might also be related to a low level of serum protein There is no convincing evidence which would indicate the precise cause

Endocrine Disturbances

These are no doubt associated with disturbed metabolism of steroids by a diseased liver In this way, oestrogens may be accumulated and give rise to such conditions as testicular atrophy and gynaecomastia Other disturbances more intimately related to the pituitary adrenal mechanism also occur and patients with cirrhosis not infrequently have diminished libido as well as sparseness of the pubic and axillary hair, with a low urinary output of ketosteroids A note of warning should be sounded here It is possible for cirrhosis especially if accompanied by skin pigmentation closely to mimic Addison s disease Myxoedema with loss of hair and eyebrows as well as skin changes has also been reported in cirrhosis

Anorexia

Unfortunately, insufficient is known about the biochemical mechanisms of appetite to give a satisfactory explanation of this very common symptom of liver disease

Metabolic Investigations Useful in Diagnosis

The chemical functions of the liver are many and varied It is intimately concerned in the metabolism of carbohydrates, fats proteins, bile acids and certain pigments It acts as an organ of excretion and of secretion It uses a variety of means of detoxication of poisonous substances prior to their excretion by the kidney

These and many other functions real and imagined have in the past been used as tests of the efficiency of the liver Most suffer from the fact that the functional reserve of the organ is so great that five sixths of its bulk can be removed without functional defect becoming apparent Often no metabolic abnormality can be demonstrated in the presence of well established disease These remarks apply especially to the tests involving alterations in carbohydrate metabolism, for example laevulose and galactose tolerance which are occasionally extremely useful but on the whole are somewhat disappointing. These tests will therefore, not be discussed further It must however be borne in mind that some of the common liver diseases are quite diffuse and affect the whole organ This is usually true of viral hepatitis and the various forms of cirrhosis The real difficulty arises in the period of incubation and the convalescent stages of a hepatitis or in a well compensated cirrhosis When the patient is jaundiced and there is no evidence of haemolysis liver disease is obvious It is in the absence of jaundice and in the presence of such vague symptoms as anorexia and fatigue in association with a palpable liver that the real problem occurs Particularly is this unfortunate, since it now appears that fairly extensive massive necrosis

may be present *without jaundice* and repeated attacks of this type will almost certainly lead to post necrotic scarring Similar remarks also apply to those forms of viral hepatitis in which the inflammatory re action is mainly in the portal tracts so called cholangiolitic hepatitis

Table 1 summarizes most of the common liver function tests Those in bold type are probably the most useful in actual practice Normal values are also given Some of these tests will now be briefly described Especial attention is given to those concerned with protein metabolism since clinical experience has demonstrated their reliability

The Serum Proteins

These may be investigated quantitatively by the older precipitation methods or by the newer techniques of electrophoresis The former usually depend on the fact that the globulins are precipitated by half saturation with ammonium sulphate leaving the albumins in solution Other precipitating agents are also used It is quite simple to determine the amount of protein in either the precipitate or the solution by a variety of chemical methods In both acute and chronic liver disease there is a tendency to hypoproteinaemia mainly at the expense of the albumin The albumin globulin ratio is therefore diminished below the normal and is not infrequently lower than 1 0 Serum albumin levels below 3 5 g per cent are of clinical significance Prognosis is said to become worse as the figure falls and is believed to be critical below 2 5 g per cent

The techniques of electrophoresis depend on the fact that protein molecules in solution will migrate in an electric field The serum pro teins travel towards the anode when buffered at pH 8 6 Depending on the velocity at which they travel five definite fractions can easily be recognized Albumin which travels the fastest and then $alpha_1$ globulin $alpha_2$ globulin beta globulin and gamma globulin in descending order If plasma is used fibrinogen takes an intermediate position between beta and gamma globulin It is now possible to carry out this type of separation on a strip of filter paper which has been soaked in buffer solution A very small amount of serum is applied in a narrow band across the strip and the current passed for some sixteen hours The proteins are fixed upon the strip by heating in an oven for half an hour and the fractions rendered visible with a protein stain they appear as bands The intensity of staining of each band is related to the concentration of that particular fraction A pair of such strips is shown in Fig 3 In liver disease there is again a tendency for a diminution in the albumin The gamma globulin and beta globulins tend to be raised the latter according to some investigators occurring especially in infective hepatitis

Paper electrophoresis has proved of some use in differentiating

TABLE 1

THE COMMONER LIVER FUNCTION TESTS WITH NORMAL VALUES

Unless otherwise stated the latter are expressed as mg /100 ml

Metabolic Function Studied	*Test*	*Normal Findings*
Carbohydrate metabolism	1 Fasting blood sugar 2 Glucose tolerance 3 Galactose tolerance (*a*) Oral (*b*) Intravenous 4 Laevulose tolerance	60–110 Max 170–190 return to fasting level in 2 hrs < 3 g in urine Max blood value less than 70 Blood galactose at fasting level in 2 hrs Max rise in blood < 35 Back to fasting in 2 hrs
Fat metabolism	1 Serum cholesterol (*a*) Total (*b*) Cholesterol ester	 140–250 60–80 % of total
Protein metabolism	1 **Serum proteins** (*a*) Precipitation method (*b*) Electrophoresis 2 Flocculation reactions (*a*) **Thymol turbidity** (*b*) **Thymol flocculation** (*c*) ***Cephalin-cholesterol* flocculation** (*d*) Zinc sulphate turbidity	Albumin 4 0-5 7 g /100 ml Globulin 1 5-3 0 g /100 ml Albumin 4 1 ± 0 32 g /100 ml $\alpha_1$globulin 0 5 ± 0 09 g /100 ml α_2 ,, 0 6 ± 0 14 g /100 ml β 0·9 ± 0 28 g /100 ml γ 1 0 ± 0 0 g /100 ml 0–4 units Negative or 1 + Negative or 1 + Up to 8 units
Pigment metabolism	1 ***Serum bilirubin*** 2 **Bile pigments in urine** 3 **Urobilinogen in urine** 4 Coproporphyrin in urine 5 Faecal urobilinogen	Max 0 8 — — < 160 μg per 24 hrs 40–280 mg per 24 hrs
Detoxication conjugation	**Hippuric acid** (*a*) Oral (*b*) Intravenous	 More than 2 5 g in 4 hr urine specimen More than 0 7 g in 1 hr urine specimen
Excretory capacity	**Bromsulphthalein** **(5 mg /Kg)**	< 7 % retention at 45 min
Miscellaneous	**Plasma prothrombin** *Plasma fibrinogen* **Serum alkaline phosphatase** Serum iron Serum cholinesterase Serum transaminase	70–120 % of normal average 200–400 3–13 K A units/100 ml 80–170 μg /100 ml Depends on method used Depends on method used

The most useful tests are indicated in bold type

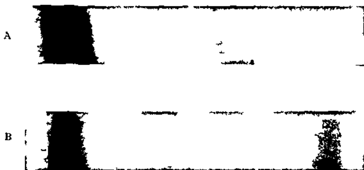


Fig 3 Results of paper strip electrophoresis of human serum A Normal B Cirrhosis In each case the albumin band is on the extreme left and the gamma globulin on the extreme right Each serum has been applied in the form of a band at the position indicated by the dots

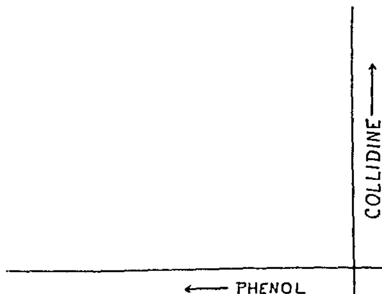


Fig 4 Normal urinary chromatogram showing only a small number of amino acid spots

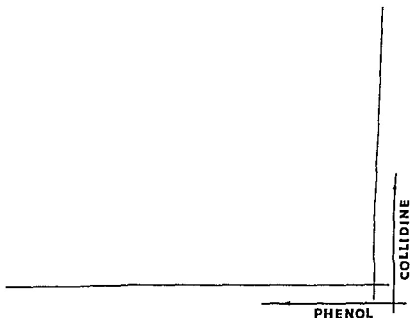


Fig 5 Urinary chromatogram from a case of acute yellow atrophy Note the large number of amino acid spots which are all well pronounced

ascites due to cirrhosis of the liver from that due to malignant infiltration of the peritoneum (Kay, 1954) In the latter condition there is frequently a well marked increase in the intensity of the band of alpha$_2$ globulin which does not occur in cirrhosis

Flocculation Tests

Though largely empirical in origin these tests have a great range of usefulness They depend on the fact that various substances produce a turbidity or a flocculation when added to serum In disease of the liver parenchyma, especially in viral hepatitis there is a marked tendency for such reactions to be above the normal range Solutions of gamma globulin alone will produce similar reactions which are much diminished by the addition of normal serum albumin Albumin from a case of viral hepatitis is said to be not nearly so efficient in this respect and so there is a greater tendency to flocculation in that disease The flocculation reactions may therefore be regarded as somewhat crude tests of serum protein pattern They may indicate an increase of gamma globulin or the presence of a non protective type of albumin There seems also a possibility that serum lipids play some part in the reactions and that the tests to some extent unmask abnormalities of these substances

The flocculation tests are named in accordance with the serum flocculating agent used We therefore have the cephalin cholesterol flocculation test the thymol turbidity and flocculation tests the zinc sulphate turbidity test and a number of others

Paper Chromatography of Urine

Paper chromatography depends on the fact that the various amino acids present in urine have different solubilities in certain solvents The procedure may be one dimensional when only one solvent is used or two dimensional when two solvents are used one after the other the second running in a direction at right angles to the first The two dimensional procedure is more useful in practice as it enables the individual amino acids to be identified by the final position they take up in the paper and by various specific colour reactions A measured small amount of urine is applied in the form of a dot near to one corner of a sheet of filter paper The solutions are now allowed successively to travel across the paper and the amino acid spots are rendered visible by spraying with ninhydrin solution which produces a colour purple as a rule with each amino acid and so gives a series of small purple areas scattered over the surface of the paper In Fig 4 a normal urine chromatogram is shown This shows only a few amino acid spots in marked contrast to the massive aminoaciduria obtained in acute yellow atrophy as shown in Fig 5 The degree of aminoaciduria is of

prognostic importance The amount shown in the figure is said to indicate a probable fatal outcome Actually the patient recovered completely after a period of coma lasting two weeks

It is opportune to point out here that crystals of leucine and tyrosine can only very occasionally be demonstrated in the urine of patients with extensive massive necrosis of the liver in spite of their classical association with the disease The paper chromatogram is a much more sensitive indicator

Bile Pigments and their Derivatives

The amount of bilirubin in the blood plasma can be determined by the well known diazo reaction associated with the name of van den Bergh It is important to emphasize that time has revealed that the differentiation into direct and indirect reactions can be very deceiving from the point of view of diagnosis The association of obstructive jaundice with a direct reaction and parenchymatous jaundice with an indirect or delayed reaction is by no means clear cut Some help has been claimed from the ratio of the quantitatively determined directly reacting pigment to that of the indirect variety

A knowledge of the total serum bilirubin content however is quite useful It helps in assessing the intensity of jaundice Prognosis tends to be more severe when the bilirubin level is unduly high Repeated determinations of the serum bilirubin are often of value One can obtain in this way so called time intensity curves For example a jaundice of total duration counted in weeks is the type associated with infective hepatitis and throughout this period other liver function tests tend to be abnormal Attacks of a fluctuating jaundice each lasting a few days with long interim periods of normal levels of serum bilirubin are indicative of cholelithiasis For a full discussion of this important topic the reader is referred to the paper by Osgood (1947)

Bilirubin can also be detected in the urine by using a variant of the diazo reaction or by the Harrison spot test In the latter barium chloride solution is added to the urine causing a precipitate of barium sulphate to be formed This adsorbs any bile pigment that may be present The precipitate is filtered off and a drop of Fouchet s reagent* allowed to fall on to the unfolded and partly dried filter paper A green colour is indicative of the presence of bile pigments This test is extremely sensitive and completely outmodes the iodine and the Gmelin tests

Urobilin can be detected in the urine by the well known Schlesinger reaction The pigment precursor urobilinogen can be detected by the Ehrlich reaction which can be rendered quantitative

These simple and often neglected tests for bile pigment and urobilin

* 1 / ferric chloride in 25 / trichloracetic acid

are highly important and are capable on occasion of giving more information than a whole battery of liver function tests

Hippuric Acid Excretion Test

This is said to investigate two functions of the liver One is its ability to mobilize glycine and the other its ability to conjugate this amino acid with benzoic acid to form hippuric acid After oral administration of 4 to 6 g of sodium benzoate the urine is collected for four hours This should contain according to older views at least 3 g of hippuric acid expressed as benzoic acid We now know this figure is too high and that patients with normal livers may excrete as little as 2 5 g For this test the kidneys must of course be able to excrete hippuric acid normally

The test seems to be falling into disuse in some centres This is a great pity since there is no doubt it is extremely useful

Serum Alkaline Phosphatase

This enzyme is derived from the osteoblasts as well as from the liver itself and is excreted in the bile In the presence of extrahepatic obstruction there is therefore a marked tendency for an increase in the blood level

Bromsulphthalein Excretion

When the dye bromsulphthalein is injected intravenously it is excreted by the liver into the duodenum Forty five minutes after the intravenous injection of 5 mg of the dyestuff per kilogram body weight less than 7 per cent should remain in the blood stream Values above this level indicate hepatic disorder Further information may be obtained by a study of the time relationships of dye disappearance from the blood as well as of its appearance in the duodenum

Bromsulphthalein excretion is an extremely useful screening test of liver function It is however not invariably abnormal in established liver disease

Serum Prothrombin Levels

On occasion great help can be obtained by determining the level of the serum prothrombin and its response to the injection of vitamin K

Diagnostic Applications of Liver function Tests

The major problems which arise are

1 In the presence of jaundice which is essentially non haemolytic are we dealing with a lesion primarily involving the liver parenchyma or with one primarily causing obstruction of the biliary system?

2 In the absence of jaundice are certain suggestive symptoms and signs manifestations of liver disease?

The first problem is largely concerned with the question of medical or surgical treatment and a mistaken conclusion may lead to a set of circumstances fraught with great danger to the patient Though the second problem also has therapeutic implications its major significance lies in prognosis It arises not only in the complete absence of a history of jaundice but also in the convalescent stage following that condition

No test or combination of tests will always give the correct solution to these problems Clinical judgment is always of the greatest importance

In the Presence of Jaundice

To decide between an obstructive or a parenchymatous lesion two simple tests are often sufficient viz the serum thymol reaction and the serum alkaline phosphatase as pointed out by Maclagan (1947) My own experience has also fully justified the usefulness of this combination of tests This is illustrated in Fig 5 Here the alkaline phosphatase is expressed as Jenner and Kay units and approximates fairly closely to similar measurements obtained by the method of King and Armstrong (1934) The thymol reaction is carried out at pH 7 55 (Latner and Pendlenton 1949) and is said to be positive if either the turbidity or the flocculation or both is raised above normal Such a reaction usually indicates the presence of primary disease of the liver parenchyma It must however be realized that a positive thymol reaction can be obtained after long-continued obstructive jaundice, and so the length of history must be taken into account in interpretation Experience has also shown that false positive reactions can be obtained in association with a continued pyrexia as well as in the reticuloses

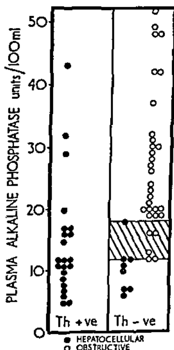


FIG 6 The plasma alkaline phosphatase in a series of cases of jaundice The results have been grouped according to the thymol reaction (from Author s M D Thesis Univ of Liverpool 1948)

A negative thymol reaction however by no means indicates the absence of primary parenchymal disease It is here that the serum alkaline phosphatase level becomes diagnostically useful

As illustrated in Fig 6 and on the basis of a much greater series of cases, I have formulated two empirical rules

1 In the presence of jaundice a positive thymol reaction usually indicates primary hepato cellular disease

2 In the presence of jaundice in association with which the thymol reaction is negative a serum alkaline phosphatase below 12 units (Jenner and Kay)/100 ml also indicates primary hepato-cellular disease whereas a serum alkaline phosphatase above 18–20 units/100 ml indicates primary obstruction to the biliary tract The diagnosis remains equivocal when the serum alkaline phosphatase lies between the two levels indicated and the thymol reaction is negative

During the last eight years in the writer s experience the application of these simple rules in the differentiation of medical from surgical jaundice has given a diagnostic accuracy upwards of 80% as proved by subsequent history liver biopsy operation or post mortem examination

In severe jaundice of any type there is a tendency for a lowering of the serum prothrombin level In hepato cellular disease this is due to the impaired synthetic ability of the liver cells It will return to normal only when the cells recover On the other hand in cases of extrahepatic obstruction the lowered prothrombin is due to impaired absorption of vitamin K from the intestine owing to the absence of bile salts Intra muscular injection of the vitamin will therefore cause a fairly rapid return of the serum prothrombin level towards normal

Another useful investigation is the determination of the serum iron level In a series of cases this tended to be above 220 μg /100 ml in the majority of cases of viral hepatitis and below this level in extra hepatic obstruction (Schamroth Edelstein Politzer and Stevens 1956) The actual diagnostic level of serum iron must be expected to vary from laboratory to laboratory and depend on the method of estimation employed All that matters is that the serum iron tends to be normal in extrahepatic obstruction and significantly raised in viral hepatitis

Recently it has been shown that in hepato cellular disease the serum transaminase level is greatly raised The estimation of this enzyme is fairly simple and the test promises to be helpful in deciding between a lesion primarily involving the liver parenchyma or one causing an obstruction of the biliary system

Having decided to which of the two main groups a jaundiced patient belongs the actual diagnosis of the lesion must remain a matter for clinical assessment which may have to include liver biopsy or laparotomy Some help may be obtained in regard to malignant obstruction by determining the urinary and fæcal urobilinogen output According to Watson (1940) absence of this pigment precursor from the urine is quite a constant finding in the malignant type but is also noted at times in calculous obstruction The latter type of case usually has a

normal faecal urobilinogen output whereas in malignant obstruction it is low extremely low or absent (5 mg or less daily)

In acute yellow atrophy one often obtains a negative thymol reaction with a low serum alkaline phosphatase If the patient recovers the flocculation tests may become positive During the acute stage of the illness if laboratory help is required in diagnosis it will be found that a massive aminoaciduria is demonstrable by paper chromatography Although as described classically the blood urea is usually very low it is not infrequently somewhat raised This is probably associated with a concomitant kidney lesion, which impairs urea excretion A sudden rise in the blood urea in a case of infective hepatitis should be regarded as possibly having a serious prognostic import

In the Absence of Jaundice

From both the clinical and the laboratory points of view liver disease without jaundice often presents much more difficulty The problem frequently arises in the incubation period of infective hepatitis while the flocculation tests are still within the normal range Much help can be obtained by simple examination of the urine which usually has an increased content of urobilinogen and often contains demonstrable bile pigment when the Harrison spot test is employed on the precipitate obtained with barium chloride It should however be remembered that several investigators have demonstrated small amounts of bilirubin in normal urines A similar state of affairs may occur in the convalescent period of the disease but here the serum flocculation tests are frequently abnormal

The bromsulphthalein-excretion test is generally considered to be the most useful as a screening test for the elimination of liver disease from a differential diagnosis Help in this respect can often be obtained from the serum flocculation reactions There seems to be some element of personal bias in relation to the individual tests It is even stated that the zinc sulphate turbidity test is more useful in chronic hepatitis whereas the thymol reactions are best in acute hepatitis The writer cannot subscribe to this view and his experience with the former test has been somewhat disappointing

The hippuric acid excretion test has proved extremely useful in the detection of liver dysfunction especially in cirrhosis In every case of low excretion kidney disease must be eliminated as a possible factor in its production Unfortunately a normal hippuric acid excretion may be found while active liver disease is present

Not infrequently some help may also be obtained by estimation of the serum alkaline phosphatase This is usually somewhat raised in the presence of cirrhosis or of liver metastases Care must of course be taken to exclude other causes of increase of this enzyme in the serum

e g vitamin deficiency or bone disease An interesting finding is the tendency to a rise in this serum component in association with chole cystitis and cholelithiasis especially if a stone is obstructing the cystic duct A similar rise occurs in dogs after cholecystectomy and is believed to be conditioned by the rise in pressure in the biliary system when the gall bladder has been removed The same mechanism may well be operating in the human being suffering from gall bladder disease This rise of serum alkaline phosphatase is not accompanied by decreased hippuric acid excretion In fact owing to irritation of the liver cells there may be a slightly increased excretion of this substance in the urine after ingestion of benzoate As stated already hippuric acid excretion is frequently diminished in the presence of liver cirrhosis and so the raised serum alkaline phosphatase of this condition can readily be distinguished from that occurring in gall bladder disease

Increasing experience is also demonstrating the usefulness of paper chromatography of the urine in obscure cases of liver disease Not in frequently an abnormal amino acid pattern is demonstrable

It must be emphasized that the employment of a large battery of tests often makes it difficult to see the wood for the trees In the absence of jaundice it is sufficient for most purposes to use only the test of brom sulphthalein excretion the flocculation tests the serum alkaline phos phatase and the hippuric acid excretion Occasionally it is necessary to investigate more closely the serum proteins including prothrombin and possibly fibrinogen

Naturally for some specific reason it may be necessary to use any of the large number of tests described in the literature for example the blood sugar response to adrenaline in attempting to establish a diag nosis of von Gierke s disease Even here however a positive test may also be obtained in cirrhosis and once again clinical judgment becomes important

From the surgeon s point of view it is regrettable that not much diagnostic help is obtained by chemical examination of bile collected by duodenal intubation The use in this technique of crude secretin (contaminated with cholecystokinin) gives greater promise (Duncan Harper Howat Oleesky and Varley 1952)

It must always be remembered that liver function tests are precisely what they are labelled They are tests of function alone and definitely not miraculous diagnostic procedures They cannot name the liver disease which is affecting function In so far as they indicate hepatic hypofunction they help along with other evidence to establish a diagnosis of liver disease Greater precision in diagnostic labelling must be attempted by methods more familiar to the clinician including liver biopsy if necessary and justified

The Use of Function Tests in Following Progress

Recovery is associated with a return of the tests to normal values One of the slowest to recover is the thymol reaction (See Fig 7) I thus test has become normal and the patient is symptom free th chances that complete recovery has occurred are good The slow dis appearance of cystine from the urine is also useful from this point o view and can easily be followed by paper chromatography

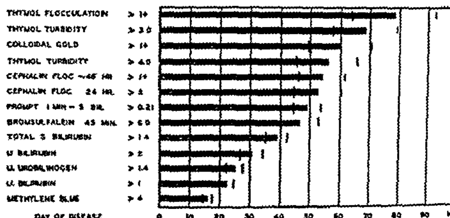


Fig 7 Average day of disappearance of individual positive tests for liver dysfunction *in cases of induced infective hepatitis (from Neefe J R and Reinhold J G Gastroenterology* 7 393 1948)

It is often stated that after an attack of infective hepatitis bed rest should be maintained until the urine is free of bile pigment

Often whilst the patient is still gravely ill it is possible to anticipate recovery from the gradual trend of the various values towards normal ity On the other hand in obstructive jaundice a fall in the plasma alkaline phosphatase towards normal in spite of a rising serum bili rubin is of ill omen and indicates the possible development of severe hepato cellular dysfunction

Therapy

General Considerations

With the exception of those conditions requiring surgical treatment and certain bacterial and protozoal infections the present treatment of liver disease is not disease specific

Therapy is mainly supportive and is aimed at providing conditions which will encourage cellular survival recovery and regeneration. The patient is therefore given adequate rest and a good supply of those nutriments which have been shown experimentally to be necessary for the survival of the normal liver cell In addition protection from known

liver toxins is provided The destruction of the viruses causing the commoner types of hepatitis is left to the patient s own immunity mechanisms In mild cases of cirrhosis it is possible that this type of regime may result in diminished fibrosis and possibly complete recovery In the vast majority of cases however the aim is to promote the health of those cells which are still surviving and functioning normally and to encourage recovery in those which are not A state of affairs can be achieved where to all intents and purposes the patient is apparently healthy This is because only a portion of the originally normal liver is required to maintain normal body metabolism An attempt is therefore made to maintain at least this portion at normal functional level When function falls below this minimum the liver may be said to be decom pensated Here it is hoped that therapy will restore sufficient cells to normal activity and regeneration and so restore the minimal function il efficiency required In the present state of our knowledge little or nothing can be done to help correct diminished function due to altered liver architecture Once this has become so abnormal as to preclude functional restoration of the requisite fractions the stage is set for the inevitable gradual downhill course so often seen in cirrhosis of any kind

We shall now consider in greater detail certain individual aspects of the supportive therapy we have been discussing

Rest

It has for a long period been believed that the most important factor in the treatment of liver disease is adequate bed rest In the cirrhotic patient it has been demonstrated that the circulation through the liver is decreased by assuming the upright position A similar mechanism may well operate in other types of disease of this organ It is well known that liver cells are particularly sensitive to oxygen deprivation a fact which emphasizes the necessity of maintaining an adequate blood supply Clinical experience in infective hepatitis has also indicated the importance during the convalescent period of graded exercise A too sudden assumption of activity may well precipitate a relapse

Recent studies in the United States Army have somewhat modified the amount of actual bed rest recommended in the treatment of un complicated viral hepatitis It is suggested that patients be kept in bed as long as acute symptoms persist and as soon as they begin to feel well they should not be forced to stay in bed for more than one hour after each meal This is regardless of the degree of jaundice Restriction to the hospital ward is however essential in order to avoid undue activity or exertion Patients may be discharged from hospital and physical reconditioning undertaken when the serum bilirubin is below 1 5 mg /100 ml and the serum bromsulphthalein 45 minute retention has been below 6% for at least one week

Carbohydrates

There is good evidence that diminution in the glycogen content of the liver renders the organ more susceptible to toxins In order to maintain the liver glycogen level there should therefore be ample administration of glucose to patients with all types of liver disease If necessary, it should be given intravenously It must be remembered that the blood sugar should be maintained at a level sufficiently high to suppress hepatic glycogenolysis This level appears to be higher in the diseased liver than in the normal organ (Portis and Weinberg, 1952) Regard less therefore of whether the patient can take food by mouth glucose should be given intravenously if the clinical condition so merits or if there is evidence of possible serious progressive deterioration This applies especially to cirrhosis and may prove useful in the treatment of ascites by making use of the diuretic effect of intravenous glucose

Protein

Because of the evidence from nutritional sources relating to the im portance of protein and certain amino acids in protecting the liver from toxins as well as promoting regeneration it is customary to increase the protein intake of patients with liver disease It is advisable to give protein containing a sufficiency of thioaminoacid For this purpose soluble casein obtained from milk is useful as a dietary supplement The aim is to give approximately 200 g of protein daily It must be remembered however that the diet should contain sufficient calories to produce a protein sparing effect A daily intake of 3500 calories is recommended This is made up largely by carbohydrate foods A note of warning however must be sounded It is now felt that in the acute stage of liver disease as in infective hepatitis, a very large protein in take may well be acting as an unnecessary strain on the capacity of a damaged organ The physician should therefore restrain his enthusi asm and preferably gradually increase protein intake during the period of convalescence Fortunately during the first few days of such an ill ness the patient s anorexia regulates this state of affairs Another pos sible danger in relation to high protein diets must be considered in cases of cirrhosis Nitrogenous substances arising from digested protein may be responsible for at least some of the neurological complications (Sherlock Summerskill White and Phear 1954)

Some authorities also recommend intravenous protein hydrolysates The writer has never really convinced himself of the efficiency of this form of treatment in severe liver disease

Fat

In view of the possible importance of fat soluble vitamins in liver metabolism there should not be any unnecessary restriction of fat in the

diet One should also remember the high calorific value of fatty foods and that it is almost impossible to administer adequate calories when fat is forbidden It is usually best to allow the patient to take as much as he can without producing nausea Fried fats should however be avoided since they are particularly prone to produce dyspepsia

Vitamins

It is usual to provide ample supplies of the vitamin B complex This is because of their importance in cellular oxidative mechanisms and their possible lipotropic effect as well as their effect on appetite

Vitamin K, which is so intimately concerned in the mechanism where by the liver produces prothrombin can be very useful in the therapy of jaundice In the obstructive variety there is a deficiency of bile salts in the intestine This interferes with fat absorption and consequently with that of the vitamin which is fat soluble The resultant vitamin deficiency in turn gives rise to a hypoprothrombinaemia and a bleeding tendency This would make surgical interference highly dangerous For this reason the vitamin is administered intramuscularly for a few days before operation which is performed only when the prothrombin of the blood is at a safe level On occasion if obstruction has been of long duration and there is a severe degree of liver failure with some biliary cirrhosis the injection of vitamin K will not have the desired effect Under these conditions the writer has on several occasions seen the prothrombin rise to safe levels if the vitamin is given intramuscularly for a few days along with his intravenous regime for severe liver disease to be described later It is interesting to note that the clinical impression is gaining ground that vitamin K can sometimes prove useful in preventing the haemorrhagic tendency occurring in severe parenchymatous liver disease The mechanism of its action is not at all clear as there is little or no increase in the blood prothrombin

Vitamins A and D in doses of 5000 and 1000 International Units respectively given once or twice a day are also believed to be of some value in chronic liver disease

Because of the evidence from the nutritional production of pathological livers it is perhaps advisable also to administer vitamin E

Since vitamin C is intimately concerned with important enzyme systems and is known to be important in a number of healing processes it is advisable also to ensure adequate supplies of this substance

In the writer s experience the macrocytic anaemia associated with severe liver disease has on several occasions apparently responded well to the administration of folic acid

Lipotropic Agents

Because of the evidence from nutritional experiments it is customary to give these substances to patients with chronic liver disease where

there is some possibility of fatty infiltration There are reports of improvement in patients with cirrhosis who were given daily doses of choline or methionine The latter substance may also be useful as a prophylactic for workers coming into frequent contact with hepatotoxins used in industry On the other hand it must be remembered that methionine may be converted by intestinal bacteria into a substance which can precipitate impending hepatic coma and other neurological manifestations of the failing liver (Phear *et al* 1956) Methionine is therefore not without its dangers

Electrolytes

In acute liver disease the administration of large quantities of glucose tends to lower the plasma potassium There also seems to be a more direct effect on the plasma electrolytes due to the disease itself This may in some way be related to the frequent association with a kidney tubular defect

In severe liver failure, for example the plasma potassium tends to fall to low levels (Latner, 1950 Artman and Wise 1953) In cirrhosis there is a marked tendency for retention of sodium especially if ascites is present (Layne and Schemm 1947) This may be connected with the low levels of serum albumin It is interesting however that the serum sodium in cirrhosis tends to be diminished (Schwarz Seegmiller Phillips Gabuzda and Davidson 1953) For these reasons the electrolyte content of the blood in cases with the appropriate type of liver disease should be estimated fairly frequently and the necessary salts administered to restore normality

Treatment of Ascites

In this condition 100–200 ml of 50% glucose solution can be given daily intravenously until fluid output exceeds intake At this point 300–400 ml of 25% glucose should be given daily until there is another demonstrable increase in output This is followed by 10% glucose in amounts up to six pints daily If at any time the fluid output is less than the intake it is necessary to resort to one of the more concentrated solutions

Intravenous salt free albumin has also been recommended in a dosage *of 100 ml of a 25% solution given over 45 minutes once or twice a day* The duration of the therapy is determined by the response The mechanism of action is by no means understood A considerable part of the albumin administered passes through the capillary walls and enters the ascitic fluid It may well be that this causes an expansion in the volume of the extracellular fluid which may possibly result in diminished absorption of water by the kidney tubules and a diuresis

It has also been considered advisable to restrict the sodium intake

This has been done by means of low salt diets or ion-exchange resins There is a tendency for development of the low salt syndrome and it can often be difficult to decide which is worse—the patient s disease or the results of the therapy

The writer has seen occasional excellent results with a continued high protein diet especially if combined with the use of mercurial diuretics Sherlock and her colleagues have demonstrated quantita tively the diminution of ascitic fluid on this type of regime (Atkinson Paton and Sherlock 1954) They used a dye dilution method for deter mining the volume of the fluid The salt intake was also kept low with no apparent ill effect They point out the theoretical danger of giving ammonium chloride with the mercurial diuretic to patients suffering from cirrhosis There is a possibility that the ammonium may pass into the blood stream and give rise to neurological complications including coma This fact must be constantly considered during such therapy

Paracentesis unfortunately still seems to be the most effective im mediate form of therapy Occasionally it may give rise to disastrous effects possibly related to the removal of the large quantities of salt dissolved in the ascitic fluid The frequency of its performance however may be markedly diminished by a high protein diet In fact on occasion and not too rarely paracentesis becomes no longer necessary

The writer has not been impressed by any of the recommended surgical procedures including hepatic artery ligation If however ascites is secondary to hypo albuminaemia which is being maintained by frequent gastro intestinal haemorrhage a porta-caval shunt may be useful

Treatment of Portal Hypertension

If associated with frequent haemorrhage from varices the most effective treatment of this condition is surgical with the production of a porta caval or spleno renal anastomosis The operation is said to be hazardous if the serum albumin level is below 3 g /100 ml or when the bromsulphthalein retention exceeds 35 per cent It is unwise to operate on a patient whose liver disease has progressed too far For such a patient who in any case is going to die fairly soon a massive haema temesis may well be a happy release Operation will only increase the misery of his last month or two of life

Not infrequently there is a rise in the level of the blood ammonia after a porta caval anastomosis

Treatment of Hepatic Coma

The therapy of this condition will depend on whether it is associated with severe acute liver disease or whether it is the result of a long standing cirrhosis In the former case there is a good chance that the

liver cells may recover from their acute noxa, and some form of supportive therapy is therefore indicated. In cirrhosis, however there is already some damage to the cells with impaired capacity to regenerate and marked diminution of their blood supply. Therapy here must be directed at the immediate cause of coma. Walshe (1953) believes this is at least in part due to ammonia intoxication, and therefore recommends the administration of sodium glutamate intravenously. Twenty three g. is given over a period of six hours once daily. This is based on the fact that metabolic ammonia, especially in the brain, is removed by combination with glutamic acid to form glutamine. A number of reports have however appeared which throw doubt on the effectiveness of glutamate therapy. It has recently been reported that greater success is obtained with intravenous arginine (Najarian and Harper 1956) which, by the production of ornithine, is said to have a mass-action effect on the Krebs urea cycle in the liver. This leads to the conversion of ammonia to urea. Oral neomycin has also been found to be effective in lowering the blood ammonia and restoring consciousness. The dosage used has been 8–12 g. daily but smaller amounts will probably prove effective (Najarian and Harper 1956).

In the therapy of coma associated with severe and acute liver disease, for example extensive hepatic necrosis, most authorities regard glutamate therapy as valueless. More satisfactory results have however been obtained with an intravenous supportive regime involving the administration of glucose, electrolytes, plasma, large doses of thiamin, nicotinamide and riboflavin, as well as the intramuscular administration of massive doses of tocopherol and antibiotics (Latner 1950). In 24 hours the patient receives 200 mg. thiamin, 600 mg. nicotinamide, 200 mg riboflavin and 300 mg. of tocopherol. The writer has now employed this regime in fifteen cases of coma due to severe and acute liver disease. There have been only four deaths. Amongst those who recovered, one patient had been in coma for two weeks. This is possibly the longest period ever reported of hepatic coma with recovery. It is an interesting fact that clinical follow up has revealed a remarkable absence of serious sequelae in the eleven patients who survived.

Liver Disease Associated with Other Disorders

In cases of fatty liver associated with diabetes mellitus beneficial results have been claimed by the administration of choline in doses of 3–4 g. per day. If the liver has become cirrhotic in association with this or any other disease, e.g. haemochromatosis, the treatment of the cirrhosis is as already discussed. The associated disease must of course be vigorously treated, and this is often a matter of no little difficulty.

For the prevention and treatment of liver disease associated with malnutrition, e.g. Kwashiorkor, a high protein diet is not infrequently

successful The difficulty is however the practical one of making the nutrient generally available to native children

Cortisone Therapy in Liver Disease

A number of reports have appeared relating to the use of cortisone in hepatic disorders Ducci has recommended it for the treatment of hepatic coma (Ducci and Katz 1952) It has also been used in acute and chronic hepatitis The reports have been somewhat conflicting

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CHAPTER 6

CARDIOVASCULAR ASPECTS OF METABOLIC DISEASE

D S FREDERICKSON R S GORDON AND J ORLOFF

Metabolic Disorders in the Aetiology of Heart Disease

Cardiovascular Disturbances in Hyperthyroidism

WHILE there is little evidence favouring the production of significant heart disease by the action of thyroid hormone alone the term thyro cardiac continues to be employed frequently in medical reports Andrus (1953) has reviewed the pertinent experimental and clinical studies of recent years and has described the common cardiovascular manifestations of hyperthyroidism By increasing the metabolism and oxygen consumption of the body as a whole hyperthyroidism imposes an increased work load upon the heart The large blood flow to the skin that is required for the dissipation of the excessive heat evolved adds to the burden Unless there is pre existing heart disease however or functional impairment due to advanced age the necessary increase of cardiac output can be accommodated without the development of the syndromes of congestive failure or angina There are necessarily some border line cases in which a previously latent cardiac disorder is first made manifest with the advent of hyperthyroidism and a patient whose current disorder is in the thyroid gland may then present with symptoms and signs of heart disease This situation is particularly prone to occur with toxic nodular goitre as these patients tend to be in the older age groups and to lack the nervousness and eye signs that so often serve to direct attention to the presence of Graves disease (Dobyns 1956)

Hyperthyroidism is clearly responsible for some alterations in cardiac function Palpitations constitute one of the commonest symptoms in hyperthyroid patients and signs relative to the increase in cardiac out put are usually discernible (tachycardia increased pulse pressure de creased circulation time) Auricular flutter and fibrillation are often seen and these disturbances in rhythm are felt to occur in patients without underlying heart disease and in such cases the rhythm usually reverts to normal following successful treatment of hyperthyroidism The tachycardia and alterations in rhythm are considered to be due to a direct effect of thyroid hormone on the heart and may be closely re lated to an augmentation of the actions of epinephrine and nor

epinephrine Indeed recent animal experimentation suggests that the major if not the sole effect of thyroid hormone on cardiac and extra cardiac tissues is to enhance tissue sensitivity to the effects of the ad renal medullary hormones (Brewster Isaacs Osgood and King 1956)

From the therapeutic viewpoint patients with cardiac manifestations due to hyperthyroidism should be considered separately from patients suffering primarily from heart disease Modern treatment directed at the relief of hyperthyroidism is in general highly successful and few patients are encountered in whom measures for the relief of cardiac failure are required The tachycardia and arrhythmias of hyperthyroid ism may not respond well to the administration of digitalis and its derivatives The aggravation of the effects of primary heart disease pro duced by complicating hyperthyroidism may not be recognized clinic ally particularly in cases in which the thyroid disorder is of mild degree Fortunately the currently available techniques for the evaluation of thyroid function enable the clinician to establish the presence or absence of hyperthyroidism with relative certainty whenever the question is raised and medical measures for the relief of hyperthyroid ism are safely applicable to the most serious cases of heart disease

Effects of Hypothyroidism on the Cardiovascular System

Signs and symptoms of cardiovascular dysfunction are not infre quently encountered among patients suffering from untreated myx oedema There is good evidence that pericardial effusion is common in this condition, and that it may proceed to such an extent as to cause complaints related to cardiac tamponade (Marks and Roof 1953) The usual physical and laboratory signs of effusion are elicited in such patients there is globular cardiac enlargement poor pulsation on fluoroscopic examination and typical electrocardiographic changes Diagnostic pericardial paracentesis has been performed on many myxoedematous patients although this procedure should only occa sionally be necessary for therapeutic purposes Replacement therapy for the underlying condition effects complete remission of the cardiac manifestations

There is perhaps still reason to believe that myxoedema impairs cardiac performance by some mechanism in addition to the production of pericardial fluid Autopsy data indicate that the ubiquitous protein rich oedema fluid from which myxoedema takes its name infiltrates the myocardium separating the muscle fibres Haemodynamic studies on five myxoedematous patients revealed two in whom cardiac output was more reduced than was systemic oxygen consumption giving evidence of a true functional impairment which in these cases could not be ex plained by pericardial effusion (Ellis Mebane Maresh Hultgren and Bloomfield 1952) In addition there is the question of exaggeration of

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the atherogenic process in subjects with long standing myxoedema and hypercholesterolaemia The committee of the Clinical Society of London which in 1888 published a complete survey of the clinical and autopsy findings in myxoedema at a time when treatment was not available, did not find evidence of an unusual degree of arterial degeneration in the major vessels Hypothyroidism (not total myxoedema) has also been induced therapeutically for the relief of intractable cardiac failure and angina the proponents of this procedure (Blumgart Freedberg and Kurland 1953) state that in their experience hypothyroidism does not predispose to coronary atherosclerosis in young subjects who might not be expected to have the condition otherwise Nevertheless the development of angina pectoris in myxoedematous patients being started on thyroid medication is a common clinical experience and while this symptom may not be clear-cut evidence of the presence of coronary atherosclerosis, it most assuredly does dictate the need for caution in instituting therapy which is otherwise entirely beneficial

Association of Heart Disease with Acromegaly

Excessive production of pituitary growth hormone in addition to causing the overgrowth of bone and connective tissue known as acromegaly is said to produce a visceromegaly in which the heart participates Hearts of acromegalic subjects at post mortem have been reported to be unusually large and the myocardium to show muscular hypertrophy minor degenerative changes and in some cases fibrosis Over half of one series of acromegalic subjects was found to have some clinical evidence of heart disease and cardiac dysfunction was the most frequent cause of death (Hejtmancik Bradfield and Herrman 1951) Abnormal electrocardiograms were encountered frequently with the most common disturbance being defective intraventricular conduction

The causal relationship of excessive growth hormone production to the development of heart disease cannot be considered to be established however because of the rarity of acromegaly and its tendency to occur in the age group in which unrelated cardiovascular disturbances are not infrequently encountered A review of the experience at the National Institutes of Health with acromegaly eleven cases having been examined since 1953, fails to corroborate the conclusions quoted above Seven of these patients had hearts of normal size as determined roentgenologically one of this group died and at autopsy the heart weighed 290 g Of the remaining four only one had clear-cut roentgenographic evidence of cardiomegaly This patient and one of the three border line cases had disorders other than acromegaly which could be considered adequate causes for cardiac enlargement (kyphoscoliosis and hypertension respectively)

Treatment of acromegaly presents a stubborn problem that is beyond the scope of this chapter Cardiac disturbances occurring in acromegalic subjects do not require particular differentiation from other cases of heart disease with regard to therapy

Cardiac Involvement in the Malignant Carcinoid Syndrome

Recent recognition of the malignant carcinoid syndrome as a clinical entity has necessitated the consideration of one more condition in which a metabolic derangement is associated presumably causally with disease of the heart The biochemical and clinical aspects of this condition have been discussed in a recent publication by Sjoerdsma Weissbach Terry and Udenfriend (1957) The fully developed syn drome is observed only in patients in whom metastases usually hepatic of the primary tumour have developed With large amounts of function ing tissue these patients convert great quantities of tryptophane to serotonin and manifest biochemical evidence of deficiency of the former and excess of the latter The diagnosis is best established by demonstration of excessive urinary excretion of 5 hydroxy indole acetic acid an end product of serotonin metabolism The clinical fea tures include gastro intestinal disturbances abdominal pain the pre sence of masses cutaneous flushing a persistent cyanosis without arterial oxygen unsaturation asthma and heart disease (Thorson Biörck Bjorkman and Waldenstrom 1954) The cardiac lesions are predominantly right sided although a few left sided lesions have been reported The commonest abnormalities are tricuspid insufficiency and pulmonic stenosis lesions which give rise to the usual murmurs and which when severe produce cardiac dilatation and congestive failure These valvular deformities are the result of endocardial fibrosis and in no case is there evidence of their having been present before the development of the carcinoid tumour Arrhythmias have not been reported as part of the syndrome The mechanism whereby the carcinoid tumour produces heart disease is unknown although a causal relationship can reasonably be inferred from the reproducible association of two other wise rare conditions Production of similar cardiac lesions in experi mental animals by the administration of serotonin or its metabolites has not been accomplished Therapy in this condition is generally unsatisfactory though with these slow growing tumours considerable relief may follow the surgical excision of tumour masses even though radical cure has not been achieved

Glycogen-storage Disease of the Heart

Not to be confused with the more familiar disease of von Gierke in which there is storage of glycogen in many organs especially the liver is a rare but clearly delineated condition best known as glycogen

storage disease of the heart Only fourteen published cases of this disease were accepted as authentic in a recent review (Di Sant Agnese Andersen and Mason 1950) The disturbance is probably a genetically determined inborn error of metabolism as evidenced by the occurrence of the condition in siblings Affected children manifest primarily symp toms of cardiac enlargement and congestive failure together with failure to grow and develop normally and do not survive more than one year There is no demonstrable systemic abnormality of carbo hydrate metabolism and the hypoglycaemia and lack of hypergly caemic response to epinephrine and glucagon, so typical of von Gierke s disease are not observed in glycogen storage disease of the heart (Recant 1955) Although it may be suspected in infants with crypto genic cardiac enlargement and failure in whom there is no evidence of valvular defects or abnormal communications the definitive diagnosis of the disease during life is extraordinarily difficult except when a pre vious case is known to have occurred in the same family No satisfac tory treatment of the condition is known At autopsy the heart is en larged to as much as six times normal weight the muscle fibres being infiltrated by so much glycogen as to have a lacework appearance in histologic sections There are lesser degrees of glycogen deposition in other tissues especially skeletal muscle

Haemochromatosis Involving the Heart

The diagnosis of idiopathic haemochromatosis should be borne in mind by any physician confronted with a middle aged male patient suffering from cardiac failure of obscure cause particularly if the diagnostic features somewhat resemble those of pericardial effusion Haemochromatosis is an uncommon condition accounting for only about 0 1% of all cardiac deaths There is a striking difference in sex incidence with 90% of cases occurring in males over the age of 35 At post mortem examination the hearts of these subjects show infiltration with haemosiderin fragmentation and necrosis of muscle fibres in the presence of some inflammatory cells The classic diagnostic triad of skin pigmentation liver disease and diabetes is not present in every case and as many as one in six haemochromatotic subjects may present primarily cardiac complaints Almost half of all haemochroma totics eventually develop cardiac manifestations and heart failure is the eventual cause of death of about one third Cardiac haemochromatosis may be the cause of either congestive failure or arrhythmias Physical examination and fluoroscopy give evidence of a dilated globular heart with poor pulsations and the electrocardiogram may show low voltage non specific T wave abnormalities left axis deviation or a variety of arrhythmias including auricular flutter and fibrillation ventricular tachycardia and varying degrees of conduction defect If

the diagnosis is once suspected it can be established with certainty by the demonstration of excessive haemosiderin in sternal marrow smears and in needle biopsies of the liver and by the elevation of the plasma iron level The usual measures for the treatment of congestive failure are of only transient benefit in haemochromatosis and the onset of arrhythmias may be particularly ominous Repeated phlebotomy offers the possibility of an attack on the basic cause of the cardiac disorder and Finch and Finch (1955) believe that the clinical response of haemochromatotic cardiac patients to this therapy is particularly rewarding

Cardiac Amyloidosis

It is only with reservations that one can introduce a discussion of amyloidosis into a text book on metabolic disease as there is no definable biochemical abnormality in this condition other than the presence in the tissues of an abnormal insoluble substance the chemistry of which is poorly understood The experimental biochemical and genetic aspects of the condition are discussed in an extensive review by Rukavina Block Jackson Falls Carey and Curtis (1956) There are at least two recognizable forms of amyloid disease which have in common the feature of tissue deposition of amyloid material they differ with regard to the existence of a predisposing chronic infection as well as with regard to the location of the amyloid deposits and the nature of the resulting functional disturbances Cardiac involvement is noted only in primary amyloidosis in which there is no underlying chronic infection and hence no basic therapeutic approach In a recent report (Benson and Smith 1956) it is stated that cardiac disorders constitute the commonest cause of complaints in primary amyloid disease The symptoms and signs are those of congestive failure never of angina The heart is found to be enlarged with diminished pulsations at fluoroscopy Murmurs attributable to the amyloidosis are rare Hypotension is common and may be distressing The electrocardiogram demonstrates low voltage various abnormal contours of the T waves and occasionally bundle branch block In addition involvement of skeletal and smooth muscles may result in weakness macroglossia and gastro intestinal disturbances Renal involvement is less common but may give rise to a fully developed nephrotic syndrome The diagnosis which often is not established during life may be suspected on the basis of involvement of these many organ systems and established by the biopsy demonstration of amyloid in some extracardiac tissue The Congo Red test is frequently not helpful in the recognition of primary amyloidosis The only available treatment is palliative directed at the relief of symptoms of cardiac failure by salt restriction and the administration of diuretic drugs The prognosis is uniformly poor

Cardiovascular Beri beri

Beri beri or deficiency of vitamin B_1 (aneurin thiamin) is encoun tered only rarely in areas of Western culture and here almost always in chronic alcoholics A few cases have been recorded in food faddists Outbreaks have occurred often in primitive and poverty stricken areas and under conditions of dietary deprivation (at sea or in prison camps) in otherwise healthy individuals It has been suggested that the critical level of vitamin B_1 intake necessary to prevent beri beri is 0 4 mg /1000 non fat calories, and that the cardiovascular manifestations are most likely to be encountered in active individuals with an adequate total caloric intake but a relative deficiency of the vitamin *The onset of the* condition may be acute and the course rapidly fatal The major mani festations to be noted include evidence of congestive failure with *oedema abdominal pain due to acute hepatic congestion and elevation* of venous pressure By cardiac catheterization it has been possible to demonstrate elevation of right ventricular diastolic pressure and pul monary capillary pressure (*Iseri Uhl*, *Chandler*, *Boyle* and *Myers*, 1954) The cardiac output is high as evidenced by decreased circulation time widened pulse pressure with a normal heart rate and the low systemic arteriovenous oxygen difference encountered at cardiac catheterization Walters (1953) states that hypertension may be a significant feature of the condition as the patient presents himself or may develop in the early phases of treatment Elevation of blood lactate and pyruvate levels is diagnostic Therapy is directed at the alleviation of the underlying vitamin deficiency, doses of up to 300 mg of vitamin B_1 being given daily by mouth or by injection Rest salt restriction, diuretic measures venesection and the hypotensive drugs may be employed to sustain life until the basic deficiency is alleviated digitalis and its derivatives are of little value Recovery from the con dition is usually complete though an occasional case with persistent myocardial damage has been recorded

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Metabolism of the Heart

The technique of catheterization of the coronary sinus of the human heart *in situ* has made possible a study of the biochemical behaviour of the normal and of the diseased heart The extraction of oxidizable sub strates from the blood perfusing the myocardium follows in the main the pattern that has been observed for skeletal muscle with the impor- tant exception that lactate which is usually produced by skeletal muscle is consumed in large quantities by myocardium In addition glucose pyruvate amino acids ketone bodies and fatty acids are extracted with the latter often accounting for the major part of the energy pro duction of the organ Stoichiometric calculations of the relationship of myocardial oxygen extraction to substrate extraction from the perfus ing blood (the oxygen extraction ratio) indicate that storage of energy yielding substrates by the myocardial tissue probably occurs but that storage is a relatively minor function of the normal tissue with most of the energy requirements being satisfied by continuous extraction of oxidizable materials from the blood

Biochemical abnormalities in the failing heart have been investigated repeatedly in heart lung preparations in animals and recently by coronary sinus catheterization in human patients (Olson 1956 Blain Schafer Siegel and Bing 1956) Measurements of oxygen and sub-

strate extraction have not revealed deficiencies that might explain the decreased pumping function of the heart Current thought favours the opinion that in congestive failure the heart suffers a decrease in efficiency that the conversion of phosphate bond energy to mechanical work is in some way compromised but that the basic biochemical processes leading to the production of intracellular high-energy metabolic intermediates are functioning normally

Digitalis and its derivatives have a well known but poorly understood effect in ameliorating the mechanical shortcomings of the failing heart Doses of lanatoside C which are effective in the treatment of clinical congestive failure have been found to have little if any effect on myocardial oxygen and substrate utilization (Blain Eddleman Siegel and Bing 1956) With the consumption of foodstuffs remaining the same the improvement in myocardial contractility resulting from digitalis administration must represent an alteration in efficiency with the evidence again pointing to the systems responsible for the conversion of phosphate bond energy to mechanical work as the target of digitalis effect

A considerable body of experimental evidence attests to the ability of the cardiac glycosides to alter the ionic content of heart muscle in a way which is thought to alter the contractility of the proteins contained therein Hajdu (1953) has published an extensive study of isolated frog hearts which demonstrates that the loss of small amounts of intracellular potassium a process which normally accompanies activity increases the mechanical strength of the succeeding beat If the heart is arrested re entry of the lost potassium occurs and the first few beats occurring when the heart is restarted are weak, with the amplitude of contraction gradually increasing thereafter (staircase phenomenon) The administration of low doses of digitalis or related substances inhibited the re entry of potassium and thus preserved the favourably low intracellular potassium content The administration of digitalis compounds to continuously beating mammalian hearts has been found to induce a loss of potassium as evidenced by a temporarily negative arteriovenous difference of this ion (Regan Talmers and Hellems 1956) and recently the same demonstration has been accomplished in the human heart *in situ* (Hellems Regan Talmers Christensen and Wada 1956)

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CHAPTER 7

OEDEMA IN CHRONIC CONGESTIVE HEART FAILURE

JACK ORLOFF

OEDEMA an abnormal expansion of the extracellular fluid compartment is the most characteristic abnormality in chronic congestive heart failure Although neither the precise metabolic derangement responsible for the excessive accumulation of salt and water nor the particular series of events involved in the production of oedema is known it is clear that the fundamental defect responsible for fluid retention is a disorder of renal function characterized by failure to excrete salt and water normally The physiologically sound kidney is capable of adjusting its output of water and solute with sufficient precision to maintain both the osmotic concentration of the extracellular and intracellular fluids and their respective volumes relatively constant despite wide variations in dietary intake In congestive failure, volume control by the kidney in so far as extracellular fluid is concerned is deficient normal balance between intake and output is deranged so that retention of salt and water supervenes producing weight gain and oedema Alterations in effective osmotic pressure are less notable occurring in only a small percentage of patients

Theories of Oedema Formation

Two major theories of the pathogenesis of oedema have been proposed the backward failure theory (Peters 1952) and the forward failure theory (Warren and Stead 1944) These are primarily descriptive analyses of the probable haemodynamic events in the development of oedema Though a renal abnormality is implicit in both neither theory is clearly addressed to the fundamental problem that is, the elucidation of the particular defect or alteration in renal function responsible for disturbed salt and water excretion in heart failure As will be noted below this inadequacy is merely a reflection of our limited knowledge concerning the intimate details of water and solute transport by the normal kidney

The proponents of the backward failure theory consider that the sequence of events in the development of oedema is initiated by an increase in venous pressure secondary to inadequate cardiac function

(back pressure*) and that transudation of fluid out of the vascular bed accounts for the initial expansion of the extravascular compartment This is essentially an extension of the Starling hypothesis (1909) that a balance exists between the forces maintaining fluid within the vascular tree (plasma oncotic pressure and interstitial hydrostatic pressure) and the forces tending to promote extrusion of fluid out of the vascular compartment (blood hydrostatic pressure and tissue oncotic pressure) Consequently any disequilibrium favouring the efferent forces (such as increased venous pressure) will effect a redistribution of fluid It is apparent that redistribution alone cannot account for the net fluid accumulation and weight gain of oedema Salt and water retention by the kidney is essential for this The stimulus which produces the renal abnormality is unknown although it has been suggested that inadequacy of blood volume in an unknown critical area somehow signals the kidney—perhaps via the adrenal—to retain salt and water The teleological nature of this argument is obvious

In contrast the proponents of the forward failure theory consider renal dysfunction secondary to inadequate cardiac output to be the initiating event in oedema production In this view extracellular fluid volume expansion precedes the rise in venous pressure The observed increase in blood volume in oedematous cardiacs is consistent with this hypothesis Merrill (1946) considers that a reduction in renal blood flow and glomerular filtration rate secondary to an inadequacy of cardiac output is the renal defect responsible for salt and water retention This will be discussed below Although data are insufficient to permit relegation of primacy to either theory in so far as the precise sequence of events in the development of oedema is concerned the virtue of the forward failure hypothesis is that it has refocused research on the fundamental problem of discovering the cause of the renal misdirection in heart failure

Renal Changes in Chronic Congestive Heart Failure

The following abnormalities in renal function have been observed in patients with congestive heart failure and oedema (1) a reduction in renal blood flow to approximately one half of normal (2) a reduction in glomerular filtration rate to approximately two thirds of normal (3) a rise in the percentage of renal blood filtered at the glomerulus † (4) an elevation in renal venous pressure (5) a diminished ability to excrete administered salt In addition it has been noted that there is

* Burch (1954) has pointed out that systemic venous pressure will not rise as a consequence of obstruction to flow in the right heart unless there is associated venospasm and/or an increase in blood volume

† The ratio of glomerular filtration rate to renal plasma flow is called the filtration fraction The increase in this ratio is thought to be due to vasoconstriction of the efferent renal arterioles

enhanced urinary excretion of both aldosterone and antidiuretic sub stance in oedematous cardiacs The clinical observations of oliguria elevation of urine specific gravity minimal proteinuria and blood urea elevation are related to some of the above findings Although the con centration of electrolytes in plasma is undisturbed in most cardiacs in the absence of complicating disorders in many, plasma sodium con centration is at the lower limits of normal and plasma potassium at the upper limits

The Mechanism of Salt and Water Excretion

Before discussing the possible significance of the above findings with respect to the pathogenesis of oedema it is necessary to review some of the present concepts concerning salt and water excretion It should be recognized that this synopsis is provisional Little is known about the intimate tubule cell mechanisms involved in salt and water transport so that what follows is largely a gross description of events as deter mined by classic clearance techniques Consequently, much of the dis cussion is necessarily hypothetical

Normally approximately 20% of the blood flowing to the kidney is filtered at the glomerulus The ultrafiltrate so formed is essentially protein free with an electrolyte concentration approaching that of the parent plasma It is thought that approximately 85% of the glomerular filtrate is reabsorbed in the proximal segment of the renal tubule as an isosmotic solution that is water and solute are reabsorbed in such a fashion that the concentration of the remaining fluid is undisturbed Sodium is thought to be abstracted by an active exchange process Attendant anion (chloride, bicarbonate etc) may be removed by virtue of the resultant electrostatic gradient or by anionic exchange Water is absorbed by simple diffusion secondary to the osmotic gradient pro duced by electrolyte abstraction The factors which determine the percentage removal of fluid in the proximal segment are not well de fined Osmotic diuretics may interfere with proximal reabsorption by diminishing the intratubular concentration of sodium and chloride The adrenal steroids which undoubtedly affect sodium and potassium transport exert their effects on an unknown portion of the tubule Furthermore although acute changes in glomerular filtration rate affect tubular reabsorption of salt and water neither the magnitude of this effect nor its direction has been determined with certainty in so far as the individual tubule segments are concerned

The remaining 15% of the original isosmotic solution is delivered to the distal segment Here most of the electrolyte and water is reabsorbed so that under normal circumstances not much more than 1% of the sodium and chloride originally present in the glomerular filtrate is excreted together with a varying percentage of water The extent of

reabsorption of electrolyte may be affected by the volume flow of proxi mal fluid by the activity of adrenal steroids and vasopressin by changes in renal venous pressure and according to some by alterations in nerve activity However all that can be stated with certainty is that both the concentration and the excretion of sodium may vary con siderably in normal individuals in the absence of appreciable changes in the concentration of sodium in plasma

As noted above patients with oedema and congestive failure generally exhibit a profound depression in blood flow to the kidney and a lesser depression in glomerular filtration rate Whether or not the fall in glomerular filtration rate is responsible *per se* for salt retention and oedema a suggestion fostered by Warren and Stead and Merrill is uncertain These workers postulated that diminished filtration of sodium in the face of essentially normal reabsorptive processes accounted for the retention of sodium chloride and water noted in heart failure Al though experimentally induced acute reductions in filtration rate are associated with a profound fall in salt excretion this observation does not necessarily constitute support for the aforesaid view Furthermore a number of situations exists in which there is a clear dissociation between the rate of glomerular filtration and salt excretion It has been observed (1) that patients may recover from the oedematous phase of heart failure without a significant rise in glomerular filtration rate (Bradley and Blake 1949) (2) that ascites may form in dogs with con striction of the thoracic inferior vena cava despite a rise in filtration rate to 50 / above the control value (Davis and Howell 1953) (3) that salt excretion may return to normal in dogs (become equal to intake) despite persistence of an experimentally reduced filtration rate (Mueller Surtshin Carlin and White 1951) The presumption is that in all of the above instances reciprocal adjustments in the tubular reabsorption of sodium whether in the proximal or distal segments may account for the re-establishment or disruption of electrolyte equilibrium

It is likely that changes in filtration rate are always associated with changes in the tubular reabsorption of sodium In addition sufficient data have accumulated to assign a significant role to alterations of tubule activity in the regulation of electrolyte transport Wide variations in electrolyte excretion may occur without measurable changes in filtration rate Furthermore Barger (1956) has demonstrated that non oedematous dogs with valvular lesions and normal filtration rates do not excrete salt injected into one renal artery as efficiently as do normal animals

Despite the above observations it should be noted that small variations in either glomerular filtration rate or tubular reabsorption may exert a considerable effect on salt balance If tubular reabsorption and plasma sodium concentration remain constant a decrease in filtra

tion rate of 1 ml/min will result in the accumulation of 1440 ml of saline in one day (1 4 Kg of weight) Similarly, an increase in proximal reabsorption from 85 to 86% of the glomerular filtrate assuming filtration rate to be 100 ml/min, will exert an equivalent effect Presently available analytical methods do not permit accurate estimates of changes of this magnitude consequently arguments as to whether tubular or glomerular factors are primarily responsible for oedema formation are unanswerable However, on the basis of all of the experimental data, it appears probable that a reduction in filtration rate must be accompanied by abnormal alterations in tubular reabsorption to effect salt retention

It has been tempting to ascribe changes of this nature in tubular reabsorption to the effects of aldosterone since it is recognized that this hormone influences sodium and potassium transport under other conditions Furthermore as noted earlier many patients with oedema have high urinary excretions of aldosterone (Luetscher and Johnson 1954) The backward failure theorists have considered that some functional change in blood volume may enhance aldosterone output and thereby produce salt retention However its influence as a primary factor is minimized and a permissive role assigned to the hormone by virtue of the observation that patients with aldosterone producing tumours are not oedematous, and further that chronic administration of salt retaining steroids to normals rather than causing salt retention produces a mild diuresis after an initial period of sodium retention The diuresis may well be due to an associated late rise in filtration rate which by increasing filtered sodium offsets any tubular effect Davis and Howell (1953) have noted that desoxycorticosterone does not diminish salt excretion chronically in dogs in whom the inferior vena cava has been constricted unless venous pressure is elevated

No discussion of heart failure would be complete without mention of the concept of a volume receptor Peters was probably the first to consider this in detail It was his view that a receptor somewhere in the body responsive to changes in volume signalled the kidney to excrete or retain salt It is probable that something of this nature may exist, otherwise it is difficult to account for the constancy of body fluid volume despite variations in salt and water intake under normal circumstances Whether such a receptor if indeed there be one is misdirected in heart failure by virtue of a deficiency in volume in some critical area as Peters considered, and oedema is due to compensatory reabsorption of electrolyte by the kidney is unknown Certainly no experimental manipulations to date have resulted in data so critical nor have the studies been so rigorously designed as to preclude the influence of any of a host of other factors (e g changes in glomerular filtration rate renal blood flow, solute excretion etc) on electrolyte excretion The

most that can be said is that the solution of the problem of the main tenance of volume is elusive albeit of signal importance

Water Excretion in Heart Failure

Water as are sodium and chloride is filtered at the glomerulus and approximately 85% reabsorbed passively as noted earlier The remaining 15% is reabsorbed to a variable extent depending upon the level of antidiuretic hormone activity and the rate of solute excretion Since considerable water is lost from the body by the non renal route (in sensible loss perspiration faeces) variations in both distal reabsorption and thirst are attuned to maintain tonicity constant The effect of changes in plasma osmotic pressure on antidiuretic hormone secretion has been described by Verney (1947) A rise in effective osmotic pressure stimulates both the desire to drink and the output of vasopressin

The current hypothesis concerning the renal mechanism of dilution and concentration and the action of vasopressin in the distal segment is complex and incomplete Smith (1956) considers that urinary dilution during antidiuretic hormone suppression is effected by the abstraction of sodium and attendant anion from isosmotic fluid in a water impermeable area Water left in the renal tubule by this process termed free water is then excreted In the presence of vasopressin the distal diluting segment becomes freely permeable to water so that as electro lyte is removed water follows passively resulting in a decrease in the volume of the isosmotic fluid initially delivered to the segment The remaining volume of isosmotic fluid is thought to pass to a terminal area (collecting duct) wherein water without electrolyte is abstracted resulting in the production of a hypertonic urine It is probable that both the diluting and concentrating mechanisms are undisturbed in the majority of oedematous patients

Peters and others ascribed a role to increased vasopressin secretion in the production of oedema Though recognizing that sodium and chloride retention was of primary importance these workers suggested that the retention of water to maintain tonicity required the interposition of excessive anti diuretic hormone activity In view of the above analysis it should be apparent that this is not essential and that in fact—were oedema due merely to an increase in reabsorption in the proximal segment—isosmotic expansion might occur in the complete absence of anti diuretic hormone In support of this is the recent observation of Laragh (1956) that dogs with diabetes insipidus accumulate ascitic fluid following caval constriction as do animals with intact pituitary glands The observation of increased urinary anti-diuretic hormone titres in cardiacs may be unrelated to the development of oedema

Water balance is regulated in a normal fashion in most oedematous cardiacs This is evidenced by normalcy of plasma tonicity and plasma

sodium concentration Even in these, water may be excreted at a lesser rate dependent on the extent of depression of filtration rate and the volume of body fluid into which the water initially diffuses A small number of patients are hyponatraemic that is have diminished plasma osmolality bespeaking hypotonic expansion of the extracellular fluid This must be a consequence of an inadequacy of the urinary diluting mechanism resulting in the retention *of water in excess of electrolyte* Although hyponatraemia has been ascribed to transfer of sodium into cells and/or bone to excessive electrolyte loss in the urine to a primary decrease in osmotic activity of cell constituents to a depression in filtration rate etc it is likely that inadequate water excretion and *extracellular dilution due to inappropriate secretion* of vasopressin is frequently responsible for the abnormality The observed urine hyper tonicity in patients with this disorder is consistent with this view It is possible that the hypothalamico hypophyseal receptor system is dis turbed since vasopressin is presumably being secreted despite diminished plasma tonicity That the receptor may be attuned to a new level is suggested by the observation that urinary dilution may be effected in a normal manner in some hyponatraemics when water is administered (Walser and Orloff 1957) It is probable that hyponatraemia ascribed to excessive use of mercurial diuretics (the low salt syndrome) is also due to inadequate water excretion rather than to electrolyte depletion alone Thus water restriction is frequently successful in the therapy of hypo *natraemia as is osmotic diuresis which results in the abstraction* of water in excess of electrolyte from the body

Therapy of Heart Failure with Oedema

This has been discussed elsewhere and will be commented upon only briefly

The use of digitalis in heart failure is directed at the cardiac disorder *per se* Any salutary effect on the elimination of oedema is therefore secondary to an improvement in cardiac status Though the glycosides may exert a direct renal tubule effect this is not of great clinical signi ficance and is of interest *only from the pharmacological point* of view

The most important measure in the therapy of oedema is restriction *of salt intake Since electrolyte excretion occurs* albeit at a markedly reduced rate even in oedematous patients it is theoretically possible to effect the elimination of all excess extracellular fluid by limiting salt intake drastically *Most often this cannot be accomplished by* this procedure alone Rather it is possible to achieve a state of relative equilibrium with respect to intake and output so that no further pro- gression of oedema occurs Water need not be restricted except in patients with dilution hyponatraemia as noted above In this regard it is unlikely that the infusion of *hypertonic saline is ever of use in* oedema

tous cardiacs since it generally promotes thirst and further increases oedema A number of clinicians have advocated its trial in severely debilitated hyponatraemic cardiacs Although this may be necessary under certain circumstances it is more rational to restrict intake of water thus allowing for reconcentration of the extracellular compartment Hypertonic urea has been used successfully in some instances since it promotes an osmotic diuresis of water in excess of salt in oedematous patients

The most effective diuretic in congestive heart failure is organic mercury The mechanism of action is unknown though it is reasonable to assume in view of the known effect of mercury of complexing with sulphhydryl groups that it may interfere in this manner with a specific enzyme involved in either sodium or chloride transport Which of these ions is involved is uncertain although most investigators consider interference with chloride transport most likely British anti Lewisite a sulphhydryl containing agent blocks the natriuretic effect of mercury presumably by complexing with the diuretic The normal response to a single injection of salyrgan or other organic mercurials is the excretion of an essentially isotonic solution of sodium and chloride Although in man mercury interferes with tubular secretion of potassium excessive kaluresis occurs in some cardiacs following its use This is most notable in patients in whom the response in so far as weight loss is concerned is negligible Hypokalaemic alkalosis and associated hypochloraemia have been observed to develop in a small number of patients

Acidifying salts (NH_4Cl $CaCl_2$ etc) when administered for one to two days prior to the injection of mercury potentiate the diuretic effect This may be related to increased dissociation of the mercury complex It is not necessarily dependent on systemic acidosis since it may occur at a time when plasma pH and bicarbonate concentration are essentially normal Continuous administration of the acidifying agent is unnecessary for this effect and may be harmful since the salts may produce anorexia and severe metabolic acidosis—the latter occurring only when renal function is initially compromised

The administration of sodium bicarbonate interferes with the natriuretic effect of mercury For this and other reasons it has been assumed that alkalosis may account for some instances of mercurial unresponsiveness It is of interest in this regard that the effect of mercury on potassium excretion is not altered by bicarbonate

The problem of resistance to mercury has been commented on elsewhere Although a diminished filtered load of sodium which occurs when either filtration rate or plasma sodium concentration or both is depressed, may account for this in some patients most often it is not possible to delineate the reason for the failure of diuresis

Carbonic anhydrase inhibitors have been used with some degree of success in recent years These drugs interfere with the enzyme which catalyses the *intracellular hydration of* CO_2 and thereby depress urinary acidification Since hydrogen ion secretion is involved in at least three processes—(1) bicarbonate reabsorption (2) sodium re absorption and (3) potassium secretion—these inhibitors by interfer ing with acid secretion promote the excretion of sodium potassium and bicarbonate Urinary alkalinization may result in metabolic acidosis kaluresis in moderate hypokalaemia (though this is rarely of clinical significance) and natriuresis in the delivery of oedema fluid Theoretically any drug promoting delivery of sodium bicarbonate (carbonic anhydrase inhibitor) is not as useful a diuretic as one promot ing the excretion of sodium chloride (mercury) since the amounts of the respective anions in extracellular fluid are markedly different This is borne out by clinical experience One further drawback to the use of the carbonic anhydrase inhibitors is the rapid development of so called resistance This change in responsiveness is related to a fall in plasma bicarbonate and does not indicate that the inhibitory effect of the drug on acidification has ceased (Berliner and Orloff 1956) Despite the limited utility of these diuretics they may be used success fully in mild cardiacs Their greatest efficacy is in patients with cor pulmonale and respiratory acidosis since diuresis and an improvement in pulmonary status may occur The cause of the latter effect is un known A peculiar property of diamox a potent carbonic anhydrase inhibitor which merits comment, is its interference with mercurial diuresis under certain conditions Despite this it is possible that if properly spaced doses are administered these diuretics may be used sequentially with beneficial effect

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CHAPTER 8

ATHEROSCLEROSIS

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HARDENING of the arteries or arteriosclerosis is the most common fatal disease known to man It is an ancient affliction having been observed in Egyptian mummies The term is a broad one including a variety of degenerative changes in the arterial wall, the cause or causes of which are not known However there is currently some basis for consideration of one form of this disease atherosclerosis among the metabolic disorders that affect the cardiovascular system Atherosclerosis is the term usually employed by the pathologist to describe the condition in which the morphologic changes of arteriosclerosis including lipid deposition fibrosis hyalinization and eventually calcification are confined primarily to the intimal layer of the arterial wall Atherosclerosis has likewise come to signify to the clinician a distinct disease entity since the lesions frequently result in narrowing and occlusion of the coronary arteries producing angina pectoris and myocardial infarction or other symptoms due to occlusion of the aorta or other of its branches including the cerebral arteries

Atherosclerosis is extremely common in man although rare in other mammals It may be seen in the very young and roughly 50% of men at age fifty and 85% at age seventy five in the United States have been said to have moderate or advanced lesions There is considerable difference in incidence among certain population groups which will be discussed below A difference between the sexes exists for coronary artery disease which is mainly due to atherosclerosis is much less common in women than in men the frequency rates converging after the age of the menopause Hypertension appears to accelerate the development of atherosclerosis in both sexes and lesions are seen frequently in localities which may be exposed to greater hydraulic stress such as areas of bifurcation Atheromata are more often found in the pulmonary arteries in cases with evidence of sustained pulmonary hypertension The development of severe atherosclerosis in the absence of hypertension indicates that this is not a basic cause but an accelerating factor in the aetiology of the disease Conversely hypertension may be associated with other arterial lesions particularly in the media which are not properly termed atherosclerosis

There is no persuasive evidence directly relating the use of tobacco physical activity or emotional stress to the development of athero sclerosis Association with a particular body build race or heredity has been suggested but the present tendency has been to interpret such differences as due to cultural influences such as upon diet rather than to genetic influences

The preponderance of evidence today *suggests* that atherosclerosis is basically a metabolic disorder particularly a result of deranged fat metabolism This is by no means proved and certain local changes in the arterial wall which have been described by some pathologists as preceding the deposition of fat such as areas of intimal thickening or formation of fibrin thrombi may be significant precipitating events Deficiency or excess or abnormal metabolism of food substances other than fat have been investigated less thoroughly although deficiency of sulphur-containing amino acids plus cholesterol feeding have produced atheromata in cebus monkeys (Mann Andrus McNally and Stare 1953) While a possible role of the endocrine glands has not been clarified no causal relationship to atherosclerosis has been demon strated beyond that of humoral effects on fat metabolism or possibly *blood pressure Hypothyroidism can be associated with hyperchole* sterolaemia and severe atherosclerosis even in youth but no conclusive pathological study exists to prove that hypometabolism is generally accompanied by increased incidence of the disease An influence of the sex hormones suggested by the marked difference in incidence between men and pre menopausal women has so far been confined to highly interesting observations of opposite effects of oestrogens and androgens on the blood lipides and lipoproteins While diabetes confers a greater susceptibility to several forms of arteriosclerosis it in turn is accom panied by hypertension and evidence of altered fat metabolism and no primary effect of the pancreas or of the adrenal or pituitary glands has been demonstrated

The evidence that an abnormality of lipide metabolism is related to *the development of atherosclerosis in man is largely inferential and rests* mainly on the following observations (1) the atheromatous plaques contain variable amounts of cholesterol phospholipides and neutral fat (2) certain clinical conditions associated with hypercholesterol aemia are commonly accompanied by a high incidence of athero sclerosis namely diabetes mellitus and essential hypercholesterolaemia with or without xanthomatosis The same is said to be true for hypo thyroidism and the nephrotic syndrome although the issue here is controversial (3) individuals with clinical evidence of coronary artery disease have as a group elevated plasma lipide and lipoprotein values (4) there is a parallel rise in the incidence of the disease and plasma lipide levels with age and (5) lesions resembling human atherosclerosis

have been produced in the monkey rabbit and chicken by the feeding of high cholesterol diets It is of interest that focal deposits of lipide have been detected within a few hours following the intravenous injec tion of human beta lipoproteins into the rat (Bragdon Havel and Boyle 1956)

The mechanism causing the deposition of lipide in the arterial wall may involve some alteration in the state in which they are normally present in the blood The plasma lipides are relatively insoluble in the plasma water and circulate bound to protein the unesterified fatty acids to albumin and the cholesterol phospholipide and triglycerides in association with the alpha and beta globulins The lipide globulin complexes result in macromolecules called lipoproteins which may be separated by solubility differences (Cohn fractionation) electro phoresis or ultracentrifugation In general the alpha$_1$ lipoproteins which have the greatest density contain very little triglyceride and have the lowest cholesterol/phospholipide ratio The beta lipoproteins re present a spectrum of macromolecules whose cholesterol/phospho lipide ratio and proportional triglyceride content rise as the density of the molecules decreases The larger and less dense macromolecules (sometimes called the alpha lipoproteins because of their position in starch block electrophoresis) scatter light and impart turbidity to the plasma The largest such particles are the chylomicrons the form in which most exogenous fat is delivered to the blood from the thoracic duct These are normally seen only during the absorption of fat Marked lactescence of the post absorptive plasma always indicates an abnormally high level of triglyceride or neutral fat and may be seen in the nephrotic syndrome severe diabetes mellitus or the rare condi tion idiopathic hyperlipaemia Elevations also have been described accompanying acute pancreatitis and hypothyroidism The concentra tion of alpha$_1$ lipoproteins may be low in biliary cirrhosis idiopathic hyperlipaemia and possibly in atherosclerosis as represented by survivors of myocardial infarction It is helpful to the physician to remember that as a general rule when the total plasma cholesterol is elevated there will be an accompanying rise in the concentration of the beta lipoproteins When the cholesterol is elevated in the presence of clear fasting plasma the accompanying rise in beta lipoprotein concen tration will involve mainly those of higher density When the hyper cholesterolaemic plasma has visible turbidity the beta lipoproteins of lower density will be elevated as well For reasons not understood there is a tendency of patients with essential (familial) hypercholester olaemia and clear fasting plasmas to develop tendon xanthomata When the hypercholesterolaemia is associated with a rise in the trigly cerides tuberous xanthomata in the skin are more commonly seen Many patients with mixed lesions are seen and it is felt that hyper

cholesterolaemic patients may represent a spectrum involving one basic disorder rather than distinct entities Patients with essential (familial) hypercholesterolaemia have an increased tendency to develop athero sclerosis The same is possibly true for patients with idiopathic hyper lipaemia in which the plasma triglycerides are markedly elevated with or without hypercholesterolaemia

In 1950 Gofman and co-workers introduced refined techniques for use of the analytical ultracentrifuge for quantitative characterization of the beta lipoproteins into various classes according to their flotation (S_f) rate (Lindgren 1951) They have proposed that from the concen trations of certain of the S_f classes an atherogenic index may be cal culated which has predictive value in determining susceptibility to coronary artery disease and that such an index has more value than simple determination of the plasma cholesterol Unfortunately general agreement has not yet been reached concerning the relative predictive value of any plasma lipide or lipoprotein measurement and the reader is referred to the original work describing such a comparison (*Report* 1956) It should be remembered that atherosclerotic coronary artery disease may develop in the presence of plasma cholesterol or lipoprotein concentrations which are considered normal for Western Europeans and Americans Conversely elevated levels may be present for years without clinical evidence of the disease

One of the striking features of atherosclerosis is the variability of its occurrence among different population groups The incidence has been reported to be lower in Okinawans Chinese and the Bantu than in white Europeans A recent autopsy study of Japanese and American casualties in Korea indicated that American youths had far more coronary atherosclerosis (Enos Beyer and Holmes 1955) Further com parisons of populations suggest that higher content of dietary fat the plasma cholesterol level and the incidence of atherosclerosis are posi tively correlated It has recently been observed by many investigators that ingestion of highly saturated fats may raise and unsaturated fats may lower the plasma cholesterol when no excess of calories is provided suggesting that not only the *amount* but the *kind* of fat may be impor tant (Beveridge Connell and Mayer 1956) There is yet no evidence to prove however the attractive hypothesis that atherosclerosis is due to a relative deficiency of essential (unsaturated) fatty acids which are preponderant in vegetable fats and rarer in those from animal sources

There is at present no specific therapy for atherosclerosis The therapeutic attack has been restricted to medications designed to lower the plasma cholesterol or alter the lipoprotein pattern Two such medications oestrogens and heparin deserve special mention All of the oestrogenic preparations given in feminizing doses (2500 to 10 000 rat units) for four to six weeks will effect a lowering of beta lipoprotein

concentrations, a rise in the alpha lipoproteins and usually a fall in the total plasma cholesterol concentration (Barr 1953) Thus most survivors of myocardial infarction for example when given oestrogen will show a reversion of the lipoprotein pattern to that usually seen in normal pre menopausal women These oestrogenic effects are quantitatively less in essential hypercholesterolaemics and in the nephrotic syndrome and are offset by the concomitant administration of androgens Side effects including breast changes loss of libido, gastro intestinal symptoms and uterine bleeding in women place a distinct limitation on the therapeutic application of oestrogens Heparin which appears to be related to the poorly understood mechanism whereby ingested fats as chylomicrons are cleared from the blood has been reported to prolong significantly the long term survival of patients following a myocardial infarction (Engelberg Kuhn and Steinman 1956) The small but real, hazard of haemorrhage and the present cost of heparin have prevented other large scale studies with this compound

Such agents as inositol and choline have no consistent effect on serum lipides or on experimental atherosclerosis Sitosterol and other plant sterols which may inhibit absorption of dietary cholesterol can moderately lower the plasma cholesterol in some patients but rarely do so dramatically or consistently There is at present no clear cut evidence supporting the use of any particular vitamin for prevention or cure of atherosclerosis Where hypercholesterolaemia is associated with hypothyroidism, diabetes or the nephrotic syndrome treatment should be directed at the primary disease The use of thyroid hormone is unwarranted in the absence of hypometabolism

Actuarial studies in the United States have indicated that obesity is associated with a higher mortality from cardiovascular disease, and there appears to be a slight but significant correlation between obesity and higher beta lipoprotein levels It appears justifiable to recommend to all patients with clinical evidence of atherosclerosis that they eat only sufficient calories to maintain ideal weight Mounting evidence further suggests that they avoid excessive intake of fats especially those from meat whole milk products and hydrogenated oils It is now the practice in many clinics to advise all patients with a moderately elevated plasma cholesterol (above 300 mg /100 ml for example) to reduce their daily fat intake to the lowest practical level which is about 30–50 g Such a diet permits lean meat, several eggs per week liberal amounts of fruits and vegetables and skim milk products A similar diet should also properly be advised to young normocholesterolaemic patients with a strongly positive family history of hypercholesterolaemia, particularly if this has been associated with clinical evidence of athero sclerosis Whether or not the addition of unsaturated oils such as corn soya bean, cottonseed olive, sunflower or safflower seed or certain fish

oils will consistently maintain lower plasma-cholesterol levels and ultimately prevent the development of atheromata or foster the regression of existing lesions has not yet been proved

If present studies relating fat intake to the development of atherosclerosis can be confirmed, the prophylactic implications will be very broad and omnivorous man may be faced with the unpleasant choice of foreshortening either his menu or the time he has remaining to enjoy it

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CHAPTER 9

LUNG FUNCTION AND ACID BASE BALANCE

S G OWEN

IN health, pulmonary ventilation is adjusted to the metabolic requirements of the body This balance depends on the sensitivity of the medullary centre controlling respiration to changes in the carbon dioxide pressure of its environment and hence to those in the arterial blood supplying it If arterial pCO_2 tends to rise, an increased rate of discharge from the centre increases the level of alveolar ventilation and therefore the pulmonary elimination of carbon dioxide the arterial pCO which is in equilibrium with that in the alveoli is thus lowered to the point at which respiratory stimulation ceases Conversely a fall in pCO is counteracted by appropriate respiratory depression and carbon dioxide retention The system operates to stabilize arterial pCO_2 in the face of changes in the volume flow of carbon dioxide returning to the lungs in the mixed venous blood, and hence to adjust ventilation to existing carbon dioxide production Normal respiratory centre sensitivity results in an average arterial pCO_2 value of 40 mm Hg

Pathological conditions causing pulmonary insufficiency for carbon dioxide elimination disturb this relationship The concentration of carbon dioxide in alveolar air (and hence its pressure in arterial blood) rises until its product with an abnormally low volume of alveolar ventilation is equal to total carbon dioxide production Equilibrium is re established at the expense of an increase in arterial pCO (*hyper capnia*) and a consequent fall in arterial pH (*respiratory acidosis*) This state is always the result of generalized underventilation of the lungs and unless high concentrations of oxygen are breathed it is associated with a corresponding degree of pulmonary insufficiency for oxygen and with arterial anoxaemia Conditions producing it include primary depression of the central nervous mechanism controlling respiration (effect of narcotic drugs medullary failure in intracranial disease) paralysis of the respiratory muscles (poliomyelitis, myasthenia gravis) obstruction to air passages (inhalation of foreign body generalized bronchospasm) gross diminution in total lung capacity (extensive pulmonary infiltration or consolidation) *diminished in* spiratory capacity due to loss of lung elasticity (emphysema) increase in effective dead space of the lungs (badly designed breathing apparatus

emphysema) and generalized inequality in [illegible] flow [illegible] throughout the lungs (pulmonary fibrosis [illegible]). An [illegible] condition of respiratory acidosis but without [illegible], [illegible] the addition of carbon dioxide to the inspired air when [illegible] hyperventilation is unable to prevent the rise in alveolar pCO_2. [illegible] continued hypercapnia depresses the CO_2-sensitivity of the [illegible] centre and when respiratory acidosis is chronic and [illegible] the [illegible] of maintaining respiratory drive reverts partly or wholly to the [illegible] primitive aortic- and carotid body chemoreceptors which [illegible] by low levels of oxygen tension. Oxygen inhalation, by [illegible] the anoxaemic stimulus then depresses ventilation further and may allow accumulation of carbon dioxide in the body to narcotic levels.

If stimuli other than arterial pCO_2 act to increase pulmonary ventilation then this becomes excessive in relation to CO_2 production and the opposite state of *respiratory alkalosis* results. Alveolar and arterial pCO_2 levels fall and the pH in arterial blood rises. The added stimulus may be primarily cortical as in voluntary and hysterical hyperpnoea or may be due to the influence of stimulant drugs on the respiratory centre (aminophylline toxic doses of salicylates). Since respiration is sensitive to changes in arterial pH (acting on both central nervous and peripheral chemoreceptor mechanisms) in addition to and independently of those in pCO_2 primary metabolic acidosis also causes hyperventilation and a fall in arterial pCO_2 until the depressant action of the hypocapnia balances the acidotic stimulation this compensatory respiratory alkalosis limits the fall in pH. Ventilatory adjustment in the opposite direction similarly superimposes respiratory acidosis upon metabolic alkalosis. Hyperventilation resulting from the action of arterial anoxaemia on the chemoreceptors of the carotid and aortic bodies produces hypocapnia and alkalosis when the anoxaemia is not associated with carbon-dioxide retention as in the inspiratory [illegible] of high altitudes. Since carbon dioxide is some twenty [illegible] diffusible than oxygen this is also the case in uncomplicated [illegible] of lung diffusing capacity which leads to pulmonary insufficiency [illegible] oxygen alone. Localized hypoventilation of areas of the lung [illegible] of ventilation/blood flow ratios and veno arterial shunts [illegible] lung cause anoxaemia without hypercapnia provided the [illegible] major part of the lung is capable of hyperventilation [illegible] ventilation fails to restore arterial pO_2 to normal (since [illegible] only negligibly to the oxygen content of that fraction of the [illegible] which is already normally ventilated) but results in a [illegible] pCO_2 which is either normal or if the anoxaemic [illegible] siderable low

The dissociation of carbonic acid is governed by the [illegible] as defined in the Henderson Hasselbalch equation

$$\mathrm{pH} = \mathrm{pK}' + \log \frac{(\mathrm{HCO_3^-})_p}{0\;03\;\mathrm{pCO_2}} \qquad \frac{(\mathrm{mM/L})}{(\mathrm{mm\ Hg})}$$

where $(HCO_3^-)_p$ is plasma bicarbonate concentration 0 03 is the solubility coefficient of CO_2 in plasma and the expression 0 03 pCO_2 is equal to the plasma concentration of dissolved CO_2 Consideration of this three variable relationship, and of the paths of acid base displacement in blood is much simplified by its graphic expression in the *pH bicarbonate diagram* (Davenport, 1950) pH and $(HCO_3^-)_p$ are plotted on abscissa and ordinate respectively and lines of equal CO_2 pressure (i e lines connecting pairs of values for pH and $(HCO_3^-)_p$ satisfying the same pCO values) are plotted or imagined (Fig 1) The $\frac{(HCO_3^-)_p}{(H_2CO_3)_p}$ system operates at a pH too far removed from its pK value (6 1) to possess significant intrinsic buffering capacity in true plasma the latter is provided by buffer groups on the haemoglobin molecule (buffer value − 2 5 mM H^+/unit pH change/mM Hb or − 22 5 mM H^+/unit pH change in average normal blood) Since, when H_2CO_3 is buffered inside the red cell the resulting HCO_3^- equivalents re diffuse into the plasma the buffer slope can be represented on the pH bicarbonate diagram as − 22 5 mM HCO_3^-/unit pH change (AOB Fig 1) If arterial pCO changes from 40 mm Hg at which it is normally fixed

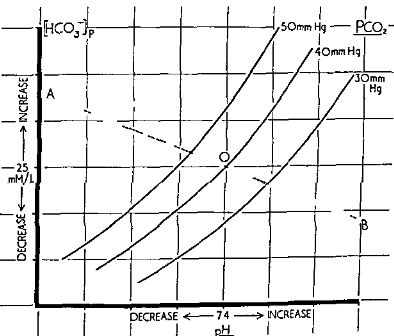


FIG 1 The pH bicarbonate diagram (after Davenport, W 1950) O = Normal equilibrium point arterial blood AOB Buffer slope (−22 5 mM HCO_3^-/unit pH change)

by the level of ventilation (point O Fig 1), the equilibrium point is titrated either up or down the buffer slope, but does not deviate from it acidity and bicarbonate concentration are increased by hypercapnia (respiratory acidosis) and decreased by hypocapnia (respiratory alkalosis) (Fig 2) The alkali reserve however, will be normal in both conditions since this is the plasma bicarbonate concentration measured after equilibration of the blood with 40 mm Hg partial pressure of carbon dioxide, i e after it has been artificially returned to point O

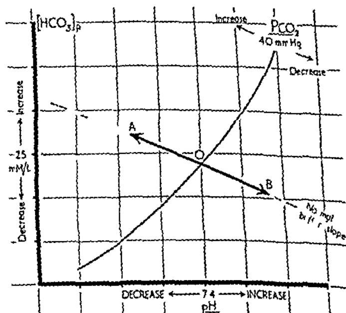


Fig 2 Paths of acid base displacement in respiratory acidosis (A) and respiratory alkalosis (B) O = normal equilibrium point of arterial blood

Non volatile or fixed acid can be neither directly buffered within the red cell nor excreted by the lungs When added to the blood, it must therefore first combine with plasma bicarbonate to form diffusib[illegible] carbonic acid this is partly eliminated by the lungs and partly b[illegible] by haemoglobin the bicarbonate corresponding to the latte[illegible] being returned to the plasma and final bicarbonate deplet[illegible] less than the total acid equivalents added If the normal rel[illegible] between alveolar ventilation and carbon-dioxide production[illegible] tained arterial pCO_2 does not alter and the condition of pur[illegible] acidosis exists the equilibrium point is displaced along the [illegible] pCO_2 isobar in the direction of depleted bicarbonate and lo[illegible] (to point C, Fig 3) In fact, the addition of compensatory [illegible]

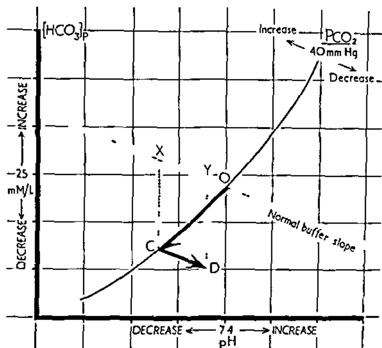


Fig 3 Paths
base displacen
pure metabolic
(C) and me
acidosis with c
satory alkalos
DY = CX = m
added O = n
equilibrium p
arterial blood

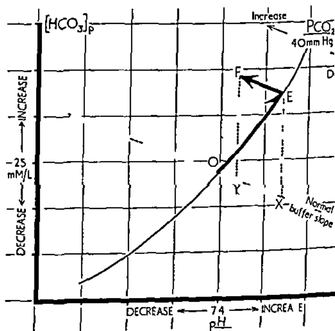


Fig 4 Paths of displacement in pure metabolic alkalosis (E) and metabolic alkalosis with compensatory respiratory acidosis (F) FY = EX = mM acid subtracted or alkali added O = normal equilibrium point of arterial blood

alkalosis as a result of acidotic hyperventilation titrates the blood from its new position down the buffer slope limiting the pH fall and further lowering the plasma bicarbonate concentration (to point D Fig 3) Equilibration with 40 mm Hg pCO will now return the blood to point C and the estimated alkali reserve is therefore low Whatever the degree of respiratory alkalosis the amount of fixed acid originally added may be estimated from the diagram as the vertical distance between the final *equilibrium point and the buffer slope in its normal position** (CX or DY Fig 3) The converse changes which take place in metabolic

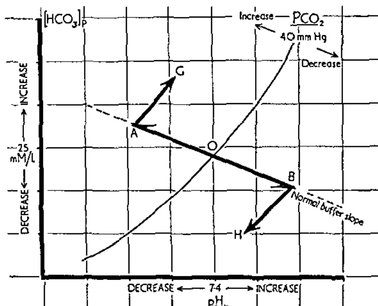


FIG 5 Paths of acid base displacement in respiratory acidosis (A) with compensatory renal metabolic alkalosis (G) and in respiratory alkalosis (B) with compensatory renal metabolic acidosis (H) O = normal equilibrium point of arterial blood

alkalosis are shown in Fig 4 Respiratory compensation for metabolic acidosis and alkalosis is never complete and does not succeed in returning the blood to the normal pH of 7 4

In chronic respiratory states of acidosis and alkalosis the ion exchange mechanism of the kidneys compensates for the change in blood pH by secreting urine of appropriate acidity Thus in respiratory alkalosis an alkaline urine of increased bicarbonate and decreased chloride concentration is separated from the blood and a metabolic acidosis is

* Or calculated by adding to the observed bicarbonate depletion the product of the observed pH change multiplied by the known value of the buffer slope

superimposed upon the original change Similarly, renal compensation adds metabolic alkalosis to primary respiratory acidosis (Fig 5) Compensation by the kidneys is usually less than complete although it may sometimes succeed in restoring blood pH to normal

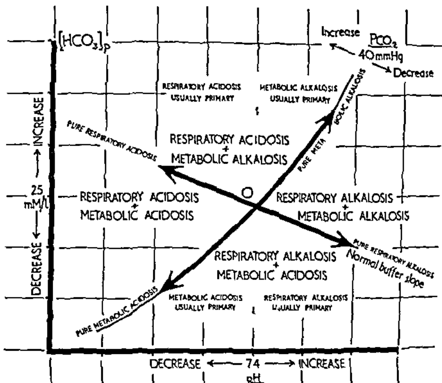


Fig 6 Possible paths of acid base displacement in arterial blood (after Davenport H W 1950) O = normal equilibrium point of arterial blood

Fig 6 summarizes the possible paths of acid base displacement in arterial blood Measurement of any two of the three variables concerned will determine the position of an arterial blood sample on the diagram and hence indicate the nature of the disturbance In the case of the upper and lower quadrants the relation of the pH to the normal value of 7 4 will decide which of the combined displacements is primary and which compensatory, since as has been pointed out neither renal nor respiratory compensation is usually complete

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CHAPTER 10

OXYGEN THERAPY

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THE practice of ogygen therapy seems to have suffered in the past because it is sometimes dramatically effective For instance when oxygen is given to a patient with severe respiratory depression his appearance improves strikingly *From this sort of experience have* come two dangerous impressions The first of these is that more benefit has been derived from the oxygen administration than is in fact the case *The marked improvement in appearance was due to the relief of* anoxaemia and the abolition of cyanosis which oxygen therapy could readily achieve in this patient but oxygen cannot alter the other con sequences of deficient ventilation and this must be remembered

The second dangerous impression is that oxygen therapy should always produce *striking* results if it is to be worth while The impression grows that unless the symptoms are flamboyant oxygen therapy is not required and that if a striking improvement is not seen on administer ing oxygen then the therapy is ineffective and should be discontinued

The facts are otherwise for the benefit from oxygen therapy will often be small and require careful study if it is to be assessed But though it may be small the benefit will often be of critical importance The need for oxygen therapy arises *when a patient or a part of the* patient is in great peril so that survival will not occur unless every advantage is gained In such critical situations even small benefit from oxygen therapy must not be disregarded for it may be impossible to obtain *this particular benefit in any other way There is no real substi* tute for oxygen in the patient s economy

THE INDICATIONS FOR OXYGEN THERAPY

It would be helpful if it were possible to set out a clear account of the pathological results of anoxia and of the signs and symptoms which give evidence of them Unfortunately this cannot be done for oxygen *is so fundamental and widespread in the body s economy that it affects* almost all systems and its lack causes disorders which can be reproduced rather than mimicked by many agents other than anoxaemia Further more anoxaemia rarely occurs alone If it be due to defective respira tion then it will necessarily be accompanied by the other consequences

of deficient ventilation notably carbon dioxide retention, and it may be accompanied by the direct effects of the agent which has caused the deficiency of ventilation for example, an overdose of a narcotic drug As another example, anoxaemia may result from respiratory obstruction when it will be accompanied by gross abnormality in intrathoracic pressure with consequent embarrassment to cardiac action facilitation of pulmonary oedema formation increased metabolic rate hypertension and very marked adrenalin release Of course there will be all of the secondary results of these disorders

Anoxia independently of the incidental disorders certainly seems to lead to disturbance of the dynamic equilibrium at interfaces which is sometimes conveniently described as their permeability Ionic balance is interfered with—as is evidenced, for example by the increased serum potassium in infants born after intra uterine anoxia, and by experimental work upon the permeability of nerve fibre Capillary membrane, subject to anoxia may become permeable to protein and oedema is a common consequence of tissue anoxia (Landis 1927 Warren Peterson and Drinker 1942 Courtice and Korner 1952) The relief of pulmonary oedema in cardiac failure may in part be due to the relief of anoxia of the pulmonary capillaries Under the influence *of anoxia capillary dilatation and blood stasis may become so gross* that escape even of red blood corpuscles may occur

Acidosis follows anoxia even when ventilation of the lungs is adequate provided that life continues long enough to permit the accumulation of fixed acids from anaerobic metabolism

The function of the liver is soon damaged by oxygen want though it is not yet possible to be sure of the proportion of effect from adrenalin release and carbon dioxide retention which so often accompany anoxia

Though the central nervous system and the conductive system of the heart seem first to suffer in acute oxygen want other organs, notably the liver or kidneys may be most seriously damaged when anoxia is less in degree but longer in duration

Analysis of the signs and symptoms of oxygen want gives us little help in the practical application of oxygen therapy

There is *no doubt whatever that anoxia affects the respiration* and a description of these effects in experimental conditions can be achieved though even then the conditions must be described precisely for the effects vary not only with the degree but also with *the rate of onset* of anoxia But there is great difficulty in deciding in clinical practice whether a particular disorder of respiration be due to oxygen want or to carbon dioxide retention or whether the oxygen want *be due to the* disorder of respiration

Experimental anoxia in normal subjects usually leads at first to a small increase in systolic and pulse pressure, followed later by accelera

tion of the heart with falling systolic pressure If there be peripheral circulatory embarrassment the first effect is not seen The degree of embarrassment produced by putting a normal subject in a vertical rather than a horizontal posture is sufficient to eliminate this early rise in pulse pressure In clinical practice the situation is much more complicated There may as an example be increased intracranial pressure when bradycardia may follow The increased intracranial pressure may be the cause of the respiratory disorder which leads to the anoxia on the other hand it may itself be the consequence of intracerebral vasodilatation due to hypercapnia springing from the same embarrassment of respiration which has led to anoxaemia

Anoxia might be expected to reveal itself characteristically through the central nervous system Amongst the symptoms are headache irritability restlessness and vomiting and in severe degree coma But other causes can produce these symptoms If a patient has received an overdose of morphine he will be anoxic—but the nausea vomiting and drowsiness from which he suffers will probably *in this instance* be unrelieved by oxygen therapy for the symptoms are due to the action of the drug rather than to the secondary anoxaemia

In practice therefore the search for characteristic signs and symptoms of anoxia will generally be fruitless Instead one must look for those disorders of function which may give rise to oxygen want and then institute oxygen therapy as a therapeutic trial The success or failure of the therapeutic trial and the continuance or discontinuance of the oxygen therapy is then determined by the response of the patient paying particular regard to improvement in the circulation respiration and nervous system Even cyanosis an apparently obvious sign of oxygen want cannot be accepted unthinkingly

Blueness of the skin and mucous membranes appears when the concentration of reduced haemoglobin in the blood circulating through the small vessels of the skin reaches a sufficient level It is the concentration of reduced haemoglobin rather than the proportion of reduced to oxygenated haemoglobin which determines the blueness Thus an anaemic person rarely becomes blue and a plethoric individual may readily become blue despite the presence of sufficient oxygenated haemoglobin

Furthermore circulation through the skin is subject to many special local influences which do not affect the circulation as a whole The rate of flow in the skin may be markedly restricted for example during chilling or it may be enormously augmented as after the administration of sedative drugs or anaesthetics In either case there may be no great change in the circulation as a whole so that the state of the blood in the skin does not faithfully reflect the state of the blood as a whole

Even if we consider only normal individuals not subject to any un

usual influence other than the reduction of the oxygen tension in the air breathed we must still recognize that many experienced observers do not detect cyanosis until the oxygenation of the arterial blood is less than 80% (Comroe and Bothelo, 1947) Thus degrees of unsaturation which are not revealed by cyanosis may be of considerable importance Donald (1953) points out that if the whole of the blood which normally passes through one lung were shunted so that it did not come into contact with the alveolar air at all saturation of the arterial blood would fall only to about 83% but there is no doubt that the patient would suffer oxygen want

It is prudent to regard cyanosis as evidence of oxygen lack unless special circumstances such as polycythaemia methaemoglobinaemia Evans blue etc are known to be present to account for the appearance The absence of cyanosis however does not give assurance that the oxygen saturation of the blood is sufficient

The situations in which oxygen therapy may be of assistance and should be tried are as follows

1 Where anoxaemia may exist because the tension of oxygen in the alveoli is low despite the respiration of normal air This may arise from a generally insufficient pulmonary ventilation as in respiratory depression or from respiratory obstruction, or from respiratory embarrassment due to thoracic or abdominal injury or disease Whenever artificial respiration becomes necessary the addition of oxygen is almost always helpful

2 When mixing of alveolar air with inspired air is imperfect because of an increase in the functional dead space, as in gross emphysema

3 When there is uneven ventilation of the lungs so that areas of lung which are perfused by blood are not fully mobile and thus are not adequately ventilated This condition can for example occur around an area of atelectasis

4 Where anoxaemia exists due to impediment to the diffusion of oxygen from the alveoli to the blood This may occur in the presence of pulmonary oedema inflammation or hyaline membrane of the lungs

5 Where help may be derived from the marked increase in oxygen tension and slight increase in oxygen content of the arterial blood which results in normal lungs from an elevation of alveolar oxygen tension above the normal level Such use of oxygen may be helpful in the following conditions

(a) Haemorrhage and shock
(b) Cardiac failure
(c) Local ischaemia for example an ischaemic limb whose survival is very precarious

The conditions of peripheral circulatory failure are so unstable

that it is hard to establish with certainty the benefit of any particular therapeutic measure Yet there is much opinion in favour of the use of oxygen in this state and provided it is done discreetly it can hardly do harm

It is true that when ventilation of the lungs is efficient replacement of nitrogen in the alveoli by oxygen can at most, increase the oxygen carried by the blood by about 1 5 volumes per cent It is worth remembering however that this effect which can be secured immediately is about equivalent in terms of oxygen carriage to the infusion of the corpuscles of a pint of blood in a normal adult Its value in cardiac failure is of course greater and in this state oxygen *therapy will have more to offer since alveolar* ventilation is often defective Though the increase in oxygen content of the blood is small oxygen inhalation will lead to a very marked increase in oxygen tension the importance of which we cannot yet assess

(*d*) Where the rapid removal of nitrogen from the body is desired as for example in the treatment of Caisson disease The use of oxygen therapy to accelerate the removal of nitrogen from the blood and therefore from gaseous distension of the gut has been advocated It is doubtful if its effect is rapid enough to be of much value

6 Where the metabolic needs of the body are increased and cannot be controlled for example in the temporary treatment of severe hyperthyroidism

In many of these instances a marked and dramatic effect cannot be expected When for example a lobe of the lung is collapsed and un ventilated but is perfused by blood no amount of oxygen therapy will achieve ventilation of the collapsed segment Since the arterial anox aemia is mainly due to the arterio venous shunt oxygen therapy cannot greatly affect it In practice however a condition of pure localized pulmonary collapse will hardly ever be seen A common situation is one in which pulmonary collapse follows an upper abdominal operation The area of collapsed lung will then frequently be associated with—(*a*) generally deficient pulmonary exchange due to abdominal pain and rigidity (*b*) incomplete aeration of lung areas bordering upon the atelectasis (*c*) the presence of secretions and exudate within the bronchioles and possibly within the alveoli (*d*) a measure of circulatory insufficiency (*e*) and there may have been haemorrhage

For this patient, the re-expansion of the collapsed lung is the primary aim of treatment but time is needed and the patient may be so critically ill that he may not survive to benefit from fundamental treatment un less something is done for him meantime

Oxygen therapy will not relieve the anoxaemia due to the pulmonary shunt but because the patient s disorder is complicated only trial can show whether it will tide him over until adequate ventilation of the whole of his lungs can be achieved This kind of situation is common and it follows that the administration of oxygen must often be regarded as a therapeutic trial If the trial is to be successful and lead to a decisive and correct conclusion two things are essential

First we must be sure that oxygen is effectively administered and second, we must know that the technique does not cause inconvenience or distress so as to outweigh the assistance of the oxygen Think for a moment of an elderly hypertensive patient who may be on the verge of coronary insufficiency and who has developed a measure of anoxaemia due, perhaps to a pulmonary infection Restlessness may well be a prominent symptom of the slight anoxaemia and one which in several ways impairs the patient s precarious chances of existence In the past one has often seen oxygen therapy given to such a patient by some quite inefficient and yet very irritating appliance such as the now completely discredited funnel method (Christie 1938) The patient was usually made worse by such treatment His irritation was increased by the presence of the funnel against his chin and nose and by the attempts which were sometimes made to immobilize his head so that it remained in some sort of relation to the funnel Whether oxygen therapy would have benefited him will never be known because in fact he received none Gestures were made with the equipment, but oxygen did not enter the patient s lungs

EQUIPMENT WHICH MAY BE USED FOR OXYGEN ADMINISTRATION

Oxygen Masks Generally speaking the administration of oxygen through a mask covering both nose and mouth is the most efficient method and concentrations up to 65–75% of oxygen in the inspired air can be achieved A great variety of oxygen masks are available and it would be profitless to describe many of them The important characteristics of a good oxygen mask are—

(*a*) It must be light in weight and equipment weighing less than 2 oz is now available

(*b*) It must be capable of fitting closely on to the face particularly of edentulous patients when the mouth is held open This is often the most difficult type of face to fit and it is not uncommon in patients needing oxygen therapy Generally speaking a mask needs to fit under the chin and some adjustment around the nose should be incorporated It is possible to make a mask fit on the anterior surface of the chin rather than under it but such a mask must usually be applied with pressure and while *it might* be

valuable in say anaesthetic work it would not be tolerable for oxygen therapy

(*c*) The appearance of the mask must be pleasant and not alarming to the patient If the patient is distressed by the mere sight of the oxygen mask the likelihood of successful administration is small

(*d*) The mask must either be easy to sterilize or must be so cheap that it can readily be thrown away when it becomes soiled or at the conclusion of an administration

The advent of plastic materials has been of great assistance in the design of oxygen masks and two are shown in Fig 1 The mask on the left consists of a non irritant plastic facepiece with a latex rubber reservoir bag and an opening to the exterior through a circular piece of metal gauze The principle of operation is as follows Let us assume that there is an adequate inflow of fresh oxygen into the reservoir bag Consider the mask at the moment when exhalation begins On exhalation the patient s dead space air first of all discharges into the reservoir bag and fills it completely since this is the outflow path of lower resistance Once the reservoir bag is completely filled the remainder of the exhalation which comprises the air which has been in contact with the alveolar membrane must take the outflow path of slightly higher resistance through the metal gauze to the exterior

On inspiration oxygen is drawn first from the reservoir bag and only when this is empty is air drawn in through the metal gauze Thus when the mask is operating correctly only dead space air is rebreathed A mask of this type is marketed in Britain by Airmed Ltd

Fig 1 (c) shows a very cheap and readily disposable oxygen mask which is fabricated from non irritant flexible plastic sheet There is in effect a small bag within a larger one The smaller inner bag forms the mask and is fitted to the face by elastic gathering below the chin and a piece of flexible wire above the nose which can be moulded to the face The outer bag forms the reservoir bag The inner bag communicates with the outer reservoir bag through holes and with the exterior air through other and rather smaller holes The principle of operation is as previously described The first part of the exhalation takes the path of the lower resistance back into the reservoir bag Once this is fully distended the remainder of the exhalation takes the path of the slightly higher resistance to the exterior A mask of this type is marketed by the British Oxygen Co Ltd (Burns and Hall 1953)

Having chosen an efficient and comfortable oxygen mask it must be used with meticulous care because it is easy to use a good oxygen mask in such a way that it is ineffective Figs 1 and 2 illustrate this point In Fig 1 (a) the mask is well adjusted and after breathing oxygen for 15 minutes at an inflow rate of 6 litres per minute the subject being at

rest an alveolar sample showed the concentration of oxygen in the alveolar air to be 62% a very substantial increase above the normal concentration In Fig 1 (b) the same mask has been allowed to ride up a little over the patient s chin but it needs more than a casual glance to decide that it is badly adjusted and such slight disturbances of positions can readily pass unnoticed in ward use With this degree of maladjustment however inhalation of oxygen at 6 litres per minute for 15 minutes resulted in an alveolar oxygen concentration of only 27%, which does not correspond with effective oxygen therapy Fig 2 (a) shows the flexible plastic inhaler correctly adjusted and 15 minutes inhalation at 6 litres a minute resulted in an alveolar concentration of 63% In Fig 2 (b) the mask is maladjusted in that the nose wire is not quite correctly moulded to the bridge of the nose The maladjustment is so slight, however that it is difficult to see in the photograph Nevertheless after 15 minutes of inhalation at 6 litres a minute the alveolar oxygen concentration was only 28%

It is clear that if oxygen administration is to be regarded on each occasion as a therapeutic trial great care must be exercised in adjusting the mask Reflection upon the manner in which oxygen is sometimes administered in hospital practice may lead us to the conclusion that apparent failure is by no means always due to the unresponsiveness of the patient s disorder to an increased alveolar oxygen tension

Given a flow of 6 litres of oxygen per minute oxygen masks of the type considered can be assumed to be working effectively when the reservoir bag remains half full at the end of inspiration and when it distends fully very early in exhalation If this condition is not seen ther are two ways of dealing with the situation The first is to secure a b tter fit upon the face and the second is to increase the rate of flow of oxygen If the mask is leaking very badly, no practicable increase in the rate of oxygen flow will secure a high enough concentration of oxygen in the inspired mixture but if the leak is slight, an increase in the rate of flow may secure effective therapy at the expense of wastefulness The increase in flow must be made if the fit cannot be improved and the slavish adherence to specified figures for oxygen flow when in fact the mask is leaking badly or when the patient is breathing excessively results in ineffective therapy

A flow meter between the cylinder and the mask is of assistance if it be intelligently used It enables one to decide whether ineffective operation of the mask as determined by the observation of the reservoir bag be due to a bad fit or to insufficient flow It must always be remembered however that if a slightly imperfect fit is all that can be secured then the oxygen flow must be increased without regard for any preconceived figures for the desirable rate A flow meter improperly regarded can be deluding



Fig 1 (*a*) A plastic mask correctly adjusted Oxygen flow 6 litres/minute Alveolar oxygen content 6



Fig 1 (*b*) Incorrectly adjusted Similar flow Alveolar oxygen content _7 The mask has risen up the chin



Fig 2 (*a*) A disposable oxygen mask correctly adjusted Flow 6 litres/minute Alveolar oxygen content 63



Fig 2 (*b*) Incorrectly adjusted Similar flow Alveolar oxygen content 28 The malleable wire is not adjusted to secure a good seal around the nose and the lower edge of the mask has moved forward so that the chin is not fully enclosed

When a mask is used the inflowing oxygen must be humidified. When released from the cylinder it is quite dry, and if an effective proportion of the inspired air is made up of this perfectly dry gas the nose, mouth and upper airway soon become dry and extremely uncomfortable. The therapy is then distressing to the patient, and even though the oxygen itself may be helpful, the over all effect of the therapy may be the reverse. It is sufficient to allow the oxygen to bubble through a bottle of water at room temperature, and in Fig. 3 there is shown a wet bubble sight flow meter which serves both as a sufficiently accurate measurement of the rate of flow and as a humidifier.

A reducing valve should always be used on the oxygen cylinder. This valve accepts the oxygen from the cylinder at high pressure and releases it into the flow meter and humidifier at a much lower pressure, which remains quite constant until the cylinder is almost empty. This lower pressure makes it much easier to control the rate of flow, and since the pressure remains constant during the cylinder's discharge, the flow adjustment does not require frequent alteration.

The Nasal Catheter. Oxygen administration by nasal catheter is less efficient than administration by mask, but there are occasions on which it is tolerated when a mask is not tolerated without distress. If therapy must be continued for some considerable time, it is often well to give the patient a change from one type of administration to another.

A urethral catheter of size depending upon the patient's build, but usually about No. 12 for an adult, is passed strictly along the floor of the nose close to the mid line, taking care that the point of the catheter does not tend to rise and touch the turbinates. It is generally helpful to lubricate the catheter with an analgesic paste and over this to put a thin layer of a much more fluid lubricating jelly. The latter assists the passage of the catheter but soon disappears and allows the analgesic paste to make tolerable the retention of the catheter. The tip of the catheter should lie behind and just below the soft palate, and should just be visible through the open mouth. It is generally easy to secure this by measuring the length of the catheter against the face, but some users advocate passing the catheter until it enters the oesophagus, which is indicated by the patient's desire to swallow, and then withdrawing it 1–1½ in. When in position the catheter must be very adequately fixed with adhesive strapping or in some other way, for it is often pulled out by a restless patient, and it is also essential that it should not be possible for the catheter to slip down and enter the oesophagus, as this may lead to inflation of the stomach. If, as often happens, the patient also has a nasal stomach tube in position, it is imperative that a method of identification which absolutely distinguishes the stomach tube from the nasal catheter be made, and explicitly impressed upon all those who will have to deal with the patient. More than one fatality has resulted from

the attachment of the oxygen supply to a stomach tube with consequent rupture of the stomach

Humidification of the oxygen is necessary and a flow meter is essential A flow of 6–8 litres a minute will be needed in the adult to secure alveolar concentration of the order of 50% It is also very desirable to have a device which prevents the building up of excess pressure should the catheter be swallowed or the oxygen flow be misconnected This may consist of a spring loaded valve on the flow meter and humidifier bottle (Fig 3) or a more sensitive blow off device of the type shown in Fig 4 Nasal catheters need frequently to be changed as they become encrusted and uncomfortable If possible, they should be changed to the other nostril, if this is available and patent

A useful alternative to the nasal catheter is the *nasal insert* described by Penefsky and Karp (1952) This is a small disc of sponge rubber which fills the anterior nares Through the disc passes a rubber catheter, which simply enters the anterior nares without penetrating deeply The authors of this device have shown that useful concentrations of oxygen in the oropharynx can be achieved by flows of the order of 7–9 litres a minute It is apparently comfortable in use and easy to apply

The ancillary equipment is similar to that needed with a nasal catheter and though the slighter lower efficiency of the device compared with the catheter and the considerably lower efficiency compared with a good oxygen mask may suggest that it would not be the first choice for administration it may be very useful when a change is necessary in the interest of the patient s comfort

Oxygen Tents Oxygen tents may conveniently be divided into two groups

(*a*) Tents which are as completely closed as possible The top and sides are made from impermeable and preferably transparent material and the lower edge of the tent is formed by a flexible curtain which must carefully be tucked in under the mattress and the patient s bed clothes The air enclosed within the tent is circulated through appropriate conditioning and absorbing chambers and is enriched in oxygen by a continuous inflow of the gas The circulation of the atmosphere within the tent may be achieved by an electrical blower or by an injector device whereby the inflowing oxygen carries along with it a considerably greater quantity of air from one part of the tent through the absorbent and conditioning chambers and back to the tent again The absorbent is usually soda lime and it removes the carbon dioxide which the patient exhales Conditioning involves cooling of the air and probably more important the removal of excess humidity This is usually achieved by passing the air over ice or sometimes over a surface kept cool by solid carbon dioxide or by electrical refrigeration Thus the operation of this type of tent may require four services an oxygen

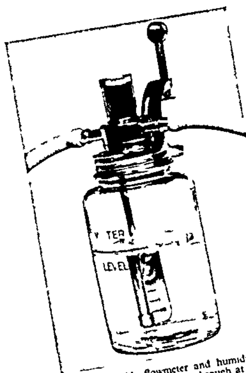


FIG 3 Bubble flowmeter and humidifier for oxygen Dry oxygen pas ing through at 6 litres minute reaches a relative humidity of about 80

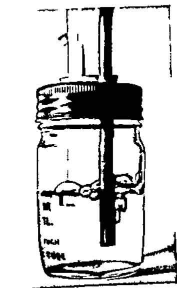


FIG 4 (*a*) Safety blow off device The device is serving as a simple flowmeter

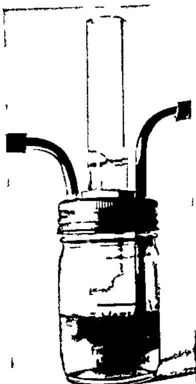


FIG 4 (*b*) Safety blow off device Excess pressure has been built up and is released by the escape of oxygen through the central tube

supply an electrical supply a supply of soda lime and a supply of ice

(*b*) The second type of oxygen tent is the open top tent which consists of a flexible canopy about 2–2½ ft high open at the top and gathered around the patient s neck and shoulders so that a substantially close seal is formed at this point Into the tent is blown a very generous supply of oxygen which needs to be of the order of 15 litres a minute This flush of oxygen is intended not only to enrich the concentration in the atmosphere breathed but to ventilate the tent sufficiently to blow away exhaled carbon dioxide and maintain a tolerable humidity The oxygen flowing into the tent should not be humidified This type of tent is particularly susceptible to draught It may work well in a cubicle but be quite inefficient if operated in the open ward or near to a window It is often necessary partially to close the top of the tent and this may frequently be done without an undue rise in carbon dioxide content of the inspired air These open top tents are difficult to use for adults though they are often very satisfactory for children up to the age of 12 when the dimensions of the enclosure can be considerably reduced and the problem of flushing the space with oxygen thus simplified

The use of either type of oxygen tent is exacting if efficient oxygen therapy is to be secured There must be meticulous attention to detail If the patient s condition is such that frequent nursing attention is needed about the head and neck it may be worthless to attempt to use an oxygen tent at all for an oxygen tent which is frequently disturbed and opened becomes merely a tent Thus unless very adequate nursing assistance is available so that all attention can be given quickly and dextrously and unless it is anticipated that the patient may remain at rest for periods of about two to three hours without disturbance it is wiser to choose some other method even though the tent is perhaps the most comfortable m thod of all

Even given suitable conditions close attention to detail is still needed For example the flexible canopy which has to be tucked under the mattress and bedclothes must be folded neatly so that it fits closely and should preferably be covered wherever possible by rubber sheeting If it is roughly and loosely tucked in success in achieving a reasonably high oxygen concentration is almost certainly forfeit

Worth while therapy depends upon achieving a concentration of oxygen of the order of 55% within the tent The patient s comfort and the prevention of deleterious effects depend upon maintaining a sufficiently low carbon-dioxide level and a sufficiently low humidity and temperature Assuming that the various containers of ice and soda lime etc are appropriately charged then if the temperature and carbon-dioxide level are sufficiently low a satisfactory humidity may be presumed for the maintenance of a low carbon-dioxide level

infers the presence of adequate ventilation Means of analysis of the inspired gas mixture are desirable with all methods of oxygen administration but some means of analysis becomes essential if an oxygen tent is intelligently to be used Jahn (1953) has demonstrated that it is impossible to predict the leakage from an oxygen tent and that periodic analysis for oxygen and carbon dioxide are indispensable

Oxygen Administration to Infants With the exception of the nasal applicator, all of the methods so far described have been adapted in miniature form for the administration of oxygen to infants Notable additions to the list are (i) the administration of oxygen to the newborn through intratracheal tubes, a measure which is used in adults only in specific emergencies and (ii) the very slow deliberate administration of oxygen by intragastric tube in the newborn in an attempt to secure the absorption of a small amount of oxygen when the lungs are incompletely expanded (Åkerren and Furstenburg 1950)

The selection of a particular method is a very individual matter depending upon the circumstances and the experience of the doctor responsible The newborn infant is extremely delicate and easily damaged, and certain of the methods mentioned are frankly dangerous This does not necessarily rule them out, but it means that no responsible doctor should embark upon their use without first learning their difficulties and dangers from someone already experienced in the practice The only method which it is safe to apply on the basis of book knowledge alone is that employing some kind of oxygen enclosure Oxygen boxes and oxygen cots of varying forms have been devised in which the whole infant is enclosed They range from specially constructed boxes designed to rest upon or enclose a mattress to a simple cover placed over a metal cot The infant s oxygen requirements are small and the space enclosed within the oxygen box is small too There is little difficulty in securing sufficiently low temperature and humidity since the infant tends to overcool rather than to overheat It is thus comparatively easy to secure within these enclosures an adequate oxygen tension with a moderate rate of flow Nevertheless such enclosures must be ventilated and they must not be completely sealed up or the carbon dioxide tension may rise to dangerous levels Some ventilating gap must be allowed between the box and the mattress or around the top of an enclosed cot Table I sets out some figures published by Mackenzie (1950) showing the influence of a ventilating gap upon oxygen and carbon dioxide tensions within a typical oxygen box

If a high oxygen concentration be secured with a low rate of inflow, it is probable that ventilation is poor and the carbon dioxide concentration high

It bears repeating that even such a simple procedure as the administration of oxygen by intranasal catheter in a newborn infant is a matter

TABLE I
BABIES OXYGEN BOX

Oxygen Flow	Ventilation Gap over Mattress	Carbon-dioxide Percentage after One Hour	Oxygen Percentage
1½ litres/min	None	1 25	65 Each figure is the mean of three trials
3 litres	None	0 85	76
3 litres	½ in	0 48	52

of considerable delicacy The catheter can be swallowed quite easily and in addition, owing to the small size of the air passages and the degree to which the faucial pillars can be approximated it is possible for the lower pharynx to become closed around the tube so that the pressure of administration is transmitted directly to the lungs and stomach Infants have been killed by overdistension of the lungs and stomach in this way and if the use of a nasal catheter be attempted it must always be in conjunction with a sensitive device which will prevent absolutely the application of pressure in excess of 10 cm of water An example of such a device is shown in Fig 4 It serves as a flow meter and humidifier and should the pressure rise more than a few cm of water the oxygen can escape freely through the large central tube

METHODS OF ANALYSIS

It is desirable to have some means of checking the efficiency of an administration of oxygen by any method However the function of an oxygen mask can usually be assessed without resorting to analysis of the pharyngeal gas The conditions of use of the nasal catheter of the nasal insert and of the oxygen enclosures used for infants can generally be standardized so that if satisfactory conditions have once been established they can be reproduced Thus with these methods ability to analyse the inspired gas mixture is desirable but not essential

When oxygen tents are used however the variability of conditions is so great that some check must be kept upon their working Many clinical instruments have been described for measuring oxygen concentration quickly and with sufficient accuracy Several are detailed fully by Barach (1944) The Riseman Lesnik analyser is one of the most convenient particularly if it is made in a slightly modified form so that the reaction chamber can be opened In clinical units where oxygen therapy is much practised some such apparatus will be available In hospitals where oxygen therapy is only occasionally applied it may occur that the apparatus is not available and cannot quickly be made The following reasonably accurate method can be carried out with equipment which is generally available in a biochemical laboratory Some form of colorimeter is needed preferably of a photo-electric

type and the only additional equipment required is an all glass syringe of 10 ml capacity, a needle and small rubber bung The method is based upon that described by Exton, Schattner, Korman and Rose (1945) for the estimation of oxygen in blood, but instead of blood a gas bubble is analysed

To standardize the size of the air bubble a small piece of glass rod is cut approximately 0 5 cm in diameter and just long enough to slip down the barrel of the syringe and lie transversely where it acts as a stop, so that when the plunger is inserted it cannot be pushed fully home but always leaves a small air space at the bottom The solutions required are as described by Exton and consist of an approximately 2% borax solution to which a little photographic wetting agent has been added, an approximately 30% solution of sulpho salicylic acid and an approximately 10% solution of ferrous sulphate, freshly prepared The solid ferrous sulphate is added to sufficient distilled water and the solution is briefly boiled It is immediately placed in centrifuge tubes and covered with paraffin and is then spun to throw down the precipitated ferric hydroxide The aqueous layer then consists of air free ferrous sulphate solution, free from any ferric salt

The needle is attached to the syringe and the syringe lubricated with borax solution A sample of gas to be analysed is drawn in either by working the plunger of the syringe to and fro several times so that the air initially present in the 'dead space' is washed out or if a very small sample is to be dealt with by filling the dead space and needle of the syringe completely with borax solution and then drawing in approximately 2 ml of the sample The syringe is now held vertically with the plunger upwards and the plunger depressed until it is stopped by the glass rod The result in either case is that the space preserved by the glass rod and the needle is filled with the sample to be analysed

Immediately this has been done the needle is put into borax solution and this is drawn in to the 2 ml mark, immediately the needle is placed into the ferrous sulphate solution below the oil and this is drawn up to the 4 ml mark Finally the ferrous sulphate solution is washed in by drawing up borax solution again, to the 8 ml mark Ejecting a little borax the needle is now firmly pushed into a rubber bung Slight pressure is exerted upon the plunger and the whole syringe shaken for three minutes The wetting agent serves to break up the air bubble into many small ones so that the oxygen rapidly dissolves in the fluid and reacts with ferrous hydroxide which has been precipitated by the borax solution when it comes into contact with the ferrous sulphate A quantity of ferric hydroxide forms which is proportional to the amount of oxygen present At the end of the three minutes 2 ml of sulpho salicylic acid are drawn into the syringe and this immediately reacts with the ferric hydroxide to produce a deep red

solution of ferric sulpho salicylate The contents of the syringe are discharged into a 500-ml flask and the syringe is repeatedly washed into the flask with distilled water The flask is made up to the mark and the concentration of the coloured solution is then such that it may conveniently be estimated in most simple photo-electric colorimeters using a green or blue filter

The method could be calibrated by making up standard solutions of ferric salts in the manner suggested by Exton *et al* (1945) For clinical purposes however it is sufficient to analyse samples of air repeatedly and also to analyse samples of 100% oxygen A blank may be done including all the reagents but no air bubble to allow for the oxygen dissolved in the reagents This is scarcely necessary in most clinical estimations as the blank is almost colourless compared with the solutions found by the analysis of air The calibration is a straight line between 0 and 100% so that the calibration line may be drawn from the known analyses of blank air and 100 / oxygen

Analysis of Air Samples for Carbon Dioxide A convenient method for repeated samples is achieved by modifying suggestions of Jones and Griffith (1944) An indicator solution is made as follows A stock solution is made by dissolving 0 15 g of methyl red in 20 ml of 95% ethyl alcohol To this is added 30 ml of 0 1 normal sodium hydroxide For use 10 ml of stock are diluted to a volume of 1 5 litres with distilled water It is convenient to take about 8 ml of the indicator solution in a colorimeter tube A simple arrangement should be made to allow the gas mixture in question to be bubbled through this indicator solution in a stream of fine bubbles A length of fine capillary tube passing through a cork which very loosely fits the colorimeter tube may be used An arrangement of a pneumatic sphygmomanometer bulb and one way valves can be made to aspirate from the area to be sampled and blow the gas directly through the colorimeter tube while it is in position in the colorimeter Alternatively the sample can be collected in an anaesthetic reservoir bag and slowly discharged through the indicator solution by squeezing the bag With the colorimeter tube already in the colorimeter the gas should be passed through the solution until the reading becomes constant The bubbling tube is then removed and the correct reading obtained The colour of the indicator changes from yellow to red and if a blue or green filter is used it will be found that the optical density will be proportional to the carbon-dioxide concentration of the gas sample between zero and 4% with this particular indicator solution Unfortunately accurate calibration can be secured only by having one standard gas sample If a small cylinder containing an accurately known concentration say 3 / of carbon dioxide be obtained the method becomes very convenient because repeated samples can then be estimated with very little trouble The calibration

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line is occasionally checked by the use of the standard cylinder In an emergency, a sample of expired air can be used for calibration its carbon dioxide content being assumed to be 4% Obviously such a calibration would be useless if the estimations were required for research purposes but it would suffice if the only purpose were to make sure that a deleterious concentration of carbon dioxide was not present in an oxygen tent

THE DANGERS OF OXYGEN ADMINISTRATION

There are certain dangers of oxygen therapy which must be discussed in physiological terms This must not blind us however to the realization that there are more mundane dangers which need to be discussed in purely physical terms Probably more people have been killed due to accidents during oxygen therapy than have been killed due to the pharmacological effects of the gas

1 It must again be stressed that there is always danger due to over distension of the lungs or inflation of the stomach with certain techniques of administration and these must carefully be guarded against There are on record several cases of death due to accidental rupture of the stomach because of the administration of oxygen under high pressure down a stomach tube

2 Deaths occur because the wrong cylinder, containing a dangerous gas is connected in place of oxygen

3 The danger of fire during oxygen administration must be stressed Commonplace materials such as woollen blankets and rubber fabrics which in the ordinary way, are barely inflammable and burn sluggishly with an easily quenchable flame, change their character completely in the presence of high oxygen tension They are then prone to burn with an intense, white rapidly spreading flame which is almost impossible to quench For example, if a blanket within an oxygen tent becomes ignited within seconds an uncontrollable conflagration has to be dealt with It cannot be too strongly stressed that attendants and relatives must be warned that they must *never* smoke or use naked lights when oxygen therapy is being carried on

4 The risks of so called oxygen poisoning when oxygen is administered at less than atmospheric pressure can largely be discounted nowadays in the generality of patients Some animal species are *much* more sensitive than man to this disorder

Experimental work on human beings has shown that continuous exposure to concentrations very close to 100% in the inspired air must be maintained for periods of about three days before the initial symptoms of oxygen poisoning appear These initial symptoms are not grave and consist of a measure of irritation of the upper respiratory tract with retrosternal pain and some excess secretions Transient headache

and dizziness have also been reported (Comroe and Dripps 1951)
Interruptions of exposure such as are almost inevitable in the clinical treatment of a patient markedly decrease the likelihood of occurrence of these symptoms Because of the availability of chemo therapy postural drainage suction clearance of secretions and so on it is now very unusual for oxygen therapy to be continued in adult patients over long periods Finally it is extremely difficult in clinical conditions to secure oxygen tensions much above 65–70% Thus it will be realized that oxygen poisoning at atmospheric pressure need not seriously concern us in normal clinical practice

5 There are certain special cases where the administration of oxygen at atmospheric pressure may have deleterious effects different from those usually described as oxygen poisoning Davies and Mackinnon (1949) have drawn attention to those patients who have an acute exacerbation of dyspnoea superimposed upon pre existing chronic bronchitis and emphysema The exacerbation is usually due to infection It seems probable that respiration is maintained in these patients largely by anoxia It is now well recognized that the oxygen tension in the blood takes its place along with the carbon-dioxide tension the hydrogen ion concentration of the blood and peripheral nervous stimulation in the maintenance of the normal quantity and rhythm of respiration (Gray 1950)

Changes in the oxygen tension of air breathed by normal people do not usually lead to marked alteration in respiration because the effect of the reduced oxygen tension is generally countered by reciprocal changes in the other quantities In the patients mentioned it seems likely that their inadequate respiration is largely maintained by the anoxial drive for their breath regulating mechanism seems over the years to have become less sensitive to the stimuli of hydrogen ion concentra tion and carbon dioxide tension and the total CO_2 content of their plasma may also be increased When the abnormal anoxia is removed by oxygen administration respiration becomes even more imperfect Anoxaemia may be reduced but the other functions of respiration are less well carried out and in particular further carbon dioxide retention occurs It may well be that this factor perhaps working through a consequent increase in cerebral blood flow is mainly responsible for the observation that these patients occasionally become comatose and show a considerable rise in cerebrospinal fluid pressure when they are given oxygen

The occurrence of these untoward symptoms is uncommon and even if they should occur they do not indicate that oxygen should altogether be denied to a patient who is apparently dying primarily of oxygen want They do mean that close observation is necessary and that the oxygen tension should be tempered to the patient s needs so as suffi

ciently to relieve the oxygen want without unduly depressing respiration Meantime of course all possible measures to secure adequate ventilation of the lungs and adequate circulatory conditions must be pursued The position seems to be well summarized in a leading article in the *Lancet* 21st February 1953 All who treat such patients should be aware of the possibility of respiratory depression, but patients must not be allowed to die of anoxia because of an exaggerated fear of carbon dioxide poisoning

Nevertheless the occurrence of these symptoms in this group of patients points to certain valuable lessons of general application We must realize first that cyanosis itself is a poor indication of the presence of anoxaemia These patients are not normal because they may have been subject for several years to chronic respiratory anoxia They may have compensated by polycythaemia, and if this has happened it is possible for them to be cyanosed and yet for the arterial oxygen content to be within the normal range since cyanosis is dependent primarily upon the quantity of reduced haemoglobin circulating in the vessels of the skin Analysis of the oxygen content of the arterial blood would be valuable

The second and more important lesson is that a 'pink' patient must not be assumed to have adequate pulmonary ventilation It is often easy by administering oxygen to secure a reassuring pinkness, to relieve anoxaemia but to leave the ventilation in an unchanged inefficient state The consequences of inefficient ventilation involve much more than anoxaemia

6 It has recently been suggested that considerable discretion should be exercised in the giving of oxygen to premature babies (*Jefferson* 1952) Retrolental fibroplasia involving the vessels of the retina and leading ultimately to blindness may develop in premature infants who have been exposed for considerable periods to high oxygen concentrations though the lesions are not detected until after the oxygen treatment has been withdrawn

Perhaps the aetiology of the condition is still imperfectly understood but prematurity and prolonged exposure to high oxygen tensions are known to be important It is unfortunate that in the small enclosures suitable for premature infants it is easy to develop high oxygen tensions *and incidentally high carbon dioxide* concentrations with relatively low gas flows

The disease must be prevented by ensuring that premature babies are not exposed to oxygen concentrations exceeding 60% when prolonged treatment is needed This moderate concentration must *not* be secured by reducing the flow of oxygen into a substantially closed box for this will lead to carbon dioxide accumulation

A simple method would be to use a moderate flow of oxygen into

an enclosure which is not completely closed so that some room air can enter some means of analysing the atmosphere in the enclosure is essential A more certain method would be to use a venturi injector device to produce a mixture of air and oxygen containing 50–60% oxygen and use the mixture to ventilate the enclosure generously

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CHAPTER 11

METABOLIC BONE DISEASE

FREDERIC C BARTTER

GENERAL CONSIDERATIONS

THE term metabolic bone disease is here used to include generalized disorders of bone wherein all the bone tissue is affected to a greater or less degree and humoral influences play a part Disorders which however widespread never affect all the bone tissue are thus considered not to be metabolic in origin (Albright and Reifenstein 1948)

The histogenesis of normal bone involves three processes—bone matrix formation bone matrix calcification and bone destruction Bone matrix is laid down by the osteoblasts by a process which in some manner involves alkaline phosphatase and the concentration of this enzyme in the serum provides in the absence of liver disease a rough index of osteoblastic activity Strains on the skeleton provide an important stimulus to osteoblastic activity Bone matrix calcification is dependent upon the calcium and phosphate ion concentrations in the fluids surrounding it and cannot occur when the product of these ions falls below a critical value Bone destruction involves the removal of the matrix and lime salts together with the participation of osteoclasts It occurs with increased rapidity in some cases of hyperparathyroidism and in some cases of renal failure, the mechanism is discussed below Normally bone is constantly being laid down and destroyed

Metabolic bone disease involving a decrease in bone mass may result from a decrease in matrix formation producing osteoporosis a decrease in matrix calcification, producing osteomalacia or rickets, or an increase in bone destruction producing osteitis fibrosa (The term osteitis fibrosa is here used instead of the cumbersome but more accurate term osteitis fibrosa cystica generalisata which would be necessary were there any possibility of its being confused with osteitis fibrosa cystica disseminata (fibrous dysplasia) which is not metabolic by our definition)

Metabolic bone disorders involving an increase in bone mass may result from an increase in matrix formation as in recently healed osteomalacia or from a decrease in bone destruction as in hypoparathyroidism and in osteopetrosis (Albers Schonberg disease) Of these hypoparathyroidism, although it may not strictly be said to produce

bone disease is discussed herein for completeness sake The aetiology of osteopetrosis a true bone disease is unknown and no rational therapy has been found

Osteoporosis

Osteoporosis develops when the rate of bone formation fails to keep pace with a normal (or indeed decreased) rate of bone destruction This will occur when the osteoblasts are inactive or when they are un able to form matrix

Factors known to stimulate osteoblastic activity are strains on the skeleton and oestrogenic hormones Thus osteoporosis develops when the skeleton is immobilized and when in the female oestrogens are withdrawn as a result of castration or the physiological menopause In ovarian agenesis where oestrogens are never present in significant quantities osteoporosis occurs at an early age

In any condition in which there is an over all loss of nitrogenous tissues in the body the counterpart in the bones would be an inability to deposit adequate matrix and osteoporosis might be anticipated This is presumably the explanation for the osteoporosis which occurs with starvation and in some patients with hyperthyroidism and dia betes—conditions in which adequate protein is not available or is diverted from structural needs in an attempt to meet caloric require ments Steroids which have the property of inducing retention of nitro gen such as testosterone have been shown to induce positive calcium balance (and thus bone matrix anabolism) in osteoporosis It is prob ably the lack of such steroids that is responsible for the osteoporosis seen in male patients with hypogonadism It is reasonable to suppose that the osteoporosis which is seen so commonly as to be almost physiological with senility is in part a result of the decline of secretion of protein anabolic steroids with age

Steroids which have the property of inducing loss of nitrogen such as cortisone with prolonged administration produce osteoporosis Here too perhaps the bone disease is the osseous manifestation of the general effects of the steroids on protein metabolism The mechanism by which these general effects are produced is not however well under stood nor can a more specific effect on matrix be excluded In Cush ing s syndrome where there is continuous overproduction of hydro cortisone osteoporosis is a prominent feature it is often seen with chronic debilitating diseases and following severe trauma—conditions in which a similar overproduction of steroids has been demonstrated

In ascorbic acid deficiency osteoporosis occurs presumably as the manifestation in the bone matrix of a generalized defect in metabolism of collagenous and cement substances

Finally there remains a group of patients with osteoporosis in whom

it is not possible to demonstrate the participation of any of the contributory factors discussed above In some the disorder may be hereditary and congenital as part of the syndrome of osteogenesis imperfecta In others it appears sporadically at any time in adult life in either sex They must for the present remain idiopathic

Clinically osteoporosis may be accompanied by pain referable to bone the most characteristic site of which is the lower back The diagnosis is often first suspected when pathological fractures occur in the vertebrae or femoral necks

Osteoporosis may be clearly distinguished histologically from other metabolic bone diseases In high magnification, osteoporotic bone resembles normal bone Few osteoblasts or osteoclasts are to be seen and all the bone matrix is calcified Under lower power (Fig 1) it is apparent that the total mass of bone is diminished The serum calcium and inorganic phosphorus are normal or the latter may be slightly high in the post menopausal state The serum alkaline phosphatase is in the low normal range These findings support the concept that the primary disorder is a failure of bone matrix formation Thus there is no disorder of calcium and phosphorus metabolism there is no evidence of increased bone destruction and in the face of a decrease of bone mass there is not as in the other metabolic bone diseases a proliferation of osteoblasts with a rise in serum alkaline phosphatase The urinary calcium excretion is frequently elevated in acute or rapidly developing osteoporosis but is often normal when the condition is well established and bone destruction is probably proceeding at a subnormal rate

Generalized radiolucency of the bones is of course common to osteoporosis osteomalacia and osteitis fibrosa There are however distinctive features whereby the first of these may often be diagnosed roentgenologically In osteoporosis the spine and pelvis may appear by X ray to be much more affected than the remainder of the skeleton whereas the skull may appear to be normal Compression fractures of vertebrae and bowing and localized rupture of the vertebral end plates are especially common The lamina dura about the teeth is preserved in osteoporosis but lost in the other two disorders Finally the bony trabeculae decreased in number may stand out with unusual clarity giving a columnar pattern to the vertebrae (Fig 2) and a filigree pattern to the pelvic bones

Although dramatic improvement in osteoporosis can seldom be demonstrated radiologically symptomatic improvement can very often be achieved by the therapeutic application of the principles discussed above Furthermore it can be shown by the balance technique that this improvement is accompanied by calcium retention and thus since bone is the only normal tissue containing appreciable calcium an increase in bone mass This applies to mobilization of the patient

in the osteoporosis of disuse to therapy with synthetic or natural oestrogens in post menopausal osteoporosis to the use of high calorie and high protein diets in the osteoporosis of starvation thyrotoxicosis or diabetes and to therapy with testosterone in the osteoporosis of eunuchoidism senility and Cushing s syndrome In the latter instance surgical cure of the primary disease may indeed lead to striking radio logic improvement as well Although no satisfactory therapy for idio pathic osteoporosis has been found (and none of the above measures is effective) there is some evidence that serum albumin intravenously administered stimulates bone matrix formation in this as in other forms of osteoporosis (Albright Forbes Bartter Reifenstein Bryant Cox and Dempsey 1950)

Certain measures are to be avoided in the treatment of osteoporosis Excessive amounts of calcium and vitamin D which have no appreci able effect on bone matrix formation (Bogdonoff Shock and Nichols 1953) may produce kidney damage or result in renal stones Unneces sary immobilization of the patient in the treatment of fractures may aggravate the underlying condition Testosterone may produce signs of masculinization in women (Methyl testosterone by linguet for example will generally do so at a dosage of 10 mg but not of 5 mg daily If the 10 mg dose is used the drug must be discontinued periodic ally) Oestrogens may produce metropathia haemorrhagica with metrorrhagia (Stilboestrol for example will generally do so at a dosage of 1 mg daily This should be avoided by withdrawal of the drug for seven to ten days at intervals of thirty five to forty days producing orderly withdrawal bleeding Decreasing the dosage of oestrogens to the point where no bleeding occurs will decrease or abolish their effectiveness on the bones)

Osteomalacia and Rickets

Osteomalacia or before epiphyseal closure rickets develops when the rate of deposition of apatite in bone matrix fails to keep pace with the rate of matrix formation This will occur when the concentration of calcium ions phosphate ions or both is low in the surrounding fluids From *in vitro* work with rachitic cartilage and from experimental work with rats it is apparent that it is the product of these ion con centrations that is critical in determining whether calcification of matrix will occur and this is supported by a large body of clinical data

Factors which may lower the serum and extracellular fluid calcium ion concentration are an inadequate calcium intake an increase of faecal calcium excretion an increase in urinary calcium excretion and of academic importance an increase in calcium excretion through breast milk In one special situation namely the healing of osteitis

fibrosa the serum calcium may be lowered by an increase in calcium deposition in bone

Osteomalacia *resulting from an inadequate calcium intake* has been reported from China and India but is not found in Europe or the Americas An increase of faecal calcium excretion may result from a failure of absorption or an increased loss of gastro intestinal secretions Vitamin D deficiency, the foremost cause of failure of calcium absorption is becoming increasingly rare in those regions where infants receive irradiated milk in formula feedings In adults it is practically confined to members of religious orders, whose clothing minimizes exposure to sunlight An interesting group of patients with so-called resistance to vitamin D will not absorb calcium unless very large doses of the vitamin are given In the sprue syndrome faecal calcium excretion is increased as a result of a calcium soap formation with un absorbed fatty acids and probably also as a result of excessive vitamin D loss, as this vitamin is carried out with unabsorbed fats In patients with prolonged diarrhoea of any cause osteomalacia may develop as the calcium of the intestinal secretions is lost to the body

The serum calcium may be lowered through an increase in urinary calcium excretion in idiopathic hypercalciuria where such calcium loss appears to result from an isolated renal disorder, and in renal tubular defects wherein tubular secretion (or, according to one view, the net renal excretion) of hydrogen ions is impaired (Latner and Burn ard 1950 Albright Burnett Parson Reifenstein and Roos 1946)

In the latter type of disorder, termed *renal tubular acidosis* cations which would normally have been replaced by hydrogen ions to neutralize urinary anions are excreted instead and potassium (and possibly magnesium) is also eliminated in increased quantities Renal tubular acidosis may appear as a unique renal lesion or in conjunction with other tubular defects as in the Fanconi syndrome The loss of calcium in breast milk is effective in lowering the serum calcium appreciably only when another cause for osteomalacia (e g dietary calcium deficiency) co exists

As discussed below the bone in osteitis fibrosa is being very rapidly destroyed and re formed When the destruction is abruptly terminated *as by removal of a parathyroid adenoma* rapid calcification of newly formed matrix may lower the serum calcium so that transient osteo malacia develops

It might be expected that osteomalacia would result from a primary *lowering of the serum phosphate ion concentration and it can* indeed be produced in experimental animals by restriction of dietary phos phate (Freeman and McLean 1941) In man osteomalacia from dietary phosphate deficiency has not been demonstrated primary renal phosphate loss is thought to produce a quite different bone *disease*

namely osteitis fibrosa cystica (It has recently been suggested that primary renal loss of phosphate can produce osteomalacia This suggestion provides no explanation for the parathyroid hyperplasia which accompanies the osteomalacia of renal tubular disease It has never been shown that such a phosphate losing lesion can exist in the absence of the parathyroids)

The aetiological factors that produce osteomalacia thus have as a *final common pathway a lowering of the serum calcium This acts as* a stimulus to the parathyroid glands to increase hormone secretion and this in turn brings about an increase in the renal excretion of phosphate (Jacobs and Verbanck 1953) with a lowering of the serum phosphate The serum is thus undersaturated with respect to calcium and phosphate with the result that (1) newly formed osteoid will not be calcified and (2) the rate of bone destruction will exceed the rate of apatite formation producing a rise of the serum calcium back towards the normal value Weakening of the bones results and the consequent increase in strains on the skeleton serves as a stimulus to the formation *of new osteoid which soon covers virtually all bone surface This latter* phenomenon may explain the persistence of some calcified bone in even the severest osteomalacia for bone once calcified is apparently never decalcified unless it can be removed altogether

Clinically osteomalacia is characterized by bone pain and tenderness more severe than that generally found in other metabolic bone diseases Positive Chvostek and Trousseau signs may be found with or without manifest tetany Weakness is often extreme even in the absence of hypokalaemia The gross deformities of the bones associated with osteomalacia in the older literature represent far advanced disease and a small minority of cases and are becoming increasingly rare as earlier diagnosis and treatment become possible Further symptoms will depend on the disorder primarily responsible for the osteomalacia fatty diarrhoea in the sprue syndrome often with symptoms referable to lack of fat soluble vitamins other than D and renal stones in essential hypercalciuria and in renal tubular acidosis sometimes in the latter condition with symptoms referable to acidosis and potassium loss

The *histological picture* (Fig 3) *of osteomalacia and rickets is* characterized by a decrease in the mass of calcified bone and a great *increase in the number of osteoblasts and in the depth and extent of* uncalcified osteoid The characteristic pseudo fractures or Umbau zones (Looser) (see below) are found to be composed of osteoid tissue with some fibrocartilage The orderly lamellar arrangement is lost in these areas and the osteoid extends characteristically beyond the *neighbouring cortex It is apparent that they represent fractures* wherein callus formation has progressed well as regards osteoid but in which calcification of the osteoid has not occurred (Looser 1920

Albright *et al*, 1946) It is evident that remodelling is held in abeyance until calcification can occur The serum calcium is normal or decreased the serum inorganic phosphate is decreased and the serum alkaline phosphatase is increased These findings support the concept that the primary disorder is a failure of bone matrix calcification Thus there is no evidence of bone destruction (osteoclasts) no decrease but rather an increase of matrix formation, and the sole abnormalities appear to be the undersaturation of the serum and the acalcification of the new matrix The urinary calcium excretion is of primary importance in determining the cause of the osteomalacia it is markedly decreased when the disorder results from failure of absorption or increased faecal excretion of calcium or from healing osteitis fibrosa and increased when the disorder results from a renal lesion

With the sprue syndrome the serum vitamin A may be decreased and the prothrombin time increased with renal tubular acidosis the serum chloride is increased and the serum carbon dioxide content and, often potassium is decreased

Whereas generalized radiolucency of the bones is found in severe osteomalacia the histological and chemical picture may be present before any changes are apparent roentgenologically The most distinctive feature of radiologic changes when they do occur is the appearance of bands of decreased density (pseudo fractures or Looser s zones) in the bones often symmetrically placed bilaterally (Fig 4) and, often extending only partially through the bone The lateral margin of the scapula is a favourite site for their appearance As discussed above they represent fractures united by uncalcified osteoid tissue They are apparently produced by very mild trauma to the bones Lemay and Blunt (1949) have suggested that in many cases an artery impinging on the bone is the effective cause of a pseudo-fracture The lamina dura about the teeth as mentioned above is lost (Fig 5) When the epiphyses are not closed they show of course the changes of true rickets (Fig 6)

Once the diagnosis of osteomalacia is made and the pathogenesis is established appropriate therapy is generally successful often producing results with surprising rapidity In all cases vitamin D and calcium will be required—very large doses of the former with resistant rickets or osteomalacia large doses of both with the sprue syndrome (if it cannot be controlled directly) With renal tubular acidosis alkali sufficient to control the acidosis must be given in addition

Two precautions in the treatment of osteomalacia are perhaps worthy of note As the bones are healed (and the serum alkaline phosphatase becomes normal) the dosage of calcium and vitamin D must be lowered before hypercalcaemia is produced The use of alkali in renal tubular acidosis should be instigated stepwise with an interval between increments sufficient to ensure that frank tetany has not been produced

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica develops when the rate of bone destruction is greatly increased This occurs in certain cases of primary hyper parathyroidism and in certain cases of renal failure with phosphate retention—predominantly in those with an associated acidosis In the former condition the primary event is clearly the overproduction of parathyroid hormone either by one or more parathyroid adenomata or in the condition known as primary hypertrophy and hyperplasia of the parathyroids by all parathyroid tissue The events which follow are (1) a decrease in renal tubular phosphate reabsorption with an increase in urinary phosphate excretion (2) a fall in the serum phosphate (3) a rise in the serum calcium and (4) a rise in the urinary calcium excretion The action of parathyroid extract in decreasing tubular reabsorption (and thus increasing renal excretion) of phosphate will account for all these changes if it be assumed that with the fall in serum phosphate undersaturation of the serum and extracellular fluids with respect to calcium and phosphate leads to a predominance in the rate of bone resorption over that of apatite formation unless the gastro intestinal tract can supply the deficit (A direct action of the parathyroids in causing bone dissolution suggested by Thompson and Collip (1932) has been demonstrated (Barnicot 1948 Chang 1951) Such an action alone will not explain the lowering of the serum phosphate nor the absence of bone disease with adequate calcium intake commonly seen in hyper parathyroidism That such an action does play a part in primary hyperparathyroidism however is indicated by the commonly observed fall in the serum phosphorus after removal of a parathyroid adenoma)

In renal failure with phosphate retention the osteitis fibrosa is regarded in this view as a complication of the metabolic abnormalities (chiefly perhaps the acidosis) resulting from the renal failure and not as a result of the secondary parathyroid hyperplasia which almost constantly co-exists Consequently removal of the parathyroid tissue in this condition is of no benefit but rather the reverse

In osteitis fibrosa of either cause bone destruction is seen as the primary event in bone This leads to a decrease in bone mass with weakening of the bones increased strains on the skeleton and a con sequent increase in bone matrix formation The newly formed matrix calcifies readily (even while bone is dissolving) probably because the phosphate concentration is raised enzymatically in the vicinity of osteoblasts

Clinically the osteitis fibrosa cystica of hyperparathyroidism differs from other metabolic bone diseases by the presence of bone cysts and tumours often visible (as in the epulis of the jaw) or palpable and these may be the sites of pathological fractures (These tumours

have been termed osteoclastomas for their abundance in the histologically striking osteoclast Actually, they contain also osteoblasts and might equally well be termed osteoblastomas) Symptoms referable to hypercalcaemia (especially anorexia nausea and vomiting) and hypercalciuria (especially renal stones) or those referable to uraemia, may of course also be present

The histological picture (Fig 7) of osteitis fibrosa cystica is characterized by a decrease in the bone mass and great increases in the number of osteoclasts and osteoblasts The marrow cavities may show fibrosis or cystic degeneration The osteoid seams are slightly if at all increased in depth The serum changes depend of course on the underlying cause of the disorder hyperparathyroidism being characterized by elevated calcium and lowered phosphate values renal failure by normal or low calcium and elevated phosphate values The serum alkaline phosphatase index of osteoblastic activity is elevated and is indeed a *sine qua non* in establishing the diagnosis These findings support the concept that the primary disorder is an increase in bone destruction Thus there is no evidence of failure of the newly formed matrix to calcify, and the osteoclast index of bone destruction is seen in large numbers only in this metabolic bone disease The serum carbon-dioxide content is generally low with renal failure when osteitis fibrosa is present The urinary calcium is almost universally elevated with hyperparathyroidism often low with renal failure

Radiologically the most characteristic findings in the osteitis fibrosa of hyperparathyroidism are the cysts especially those within the cortex which mark the site either of osteoclastomas or of true cysts For reasons not understood cortical cysts are rarely if ever seen with the osteitis fibrosa of renal failure (Pugh 1951) The skull often shows a characteristic mottled appearance and the cortex of the phalanges may show a roughened saw tooth appearance (Fig 8) where bone has been resorbed subperiosteally The lamina dura about the teeth is lost When the epiphyses are not closed osteitis fibrosa results in an irregular distortion of the epiphyseal lines often distinguishable radiologically from the smooth concave widening of these lines seen in true rickets Because of these changes the term renal rickets was early applied to this condition This unhappy choice of terms has been a source of confusion, as it not only labelled as 'rickets what was actually osteitis fibrosa but also prevented for practical purposes the use of the term for the true rickets of renal tubular acidosis

The treatment of primary hyperparathyroidism is surgical Before operation the patient should be immobilized as little as possible (to prevent a superimposed osteoporosis) and given a low calcium diet with forced fluids The extent of the bone disease should be estimated from the radiologic survey and also from the value of the serum alkaline

phosphatase which is a fairly reliable index thereto Mild post operative tetany is to be expected in the absence of bone disease but when the bones are extensively involved severe tetany must be anticipated (as a transient state of osteomalacia develops) and if possible prevented The patient should be warned that transient mental depression commonly follows the successful cure of hyperparathyroidism At operation all parathyroid glands should be visualized if possible Adenomata may be single or multiple they should of course be removed In about 10% of cases primary hyperplasia and hypertrophy of all parathyroid tissue is found If this is suspected frozen section should be made to rule out secondary hyperplasia with the former, small amounts of tissue should be left with blood supply and the rest removed with the latter none should be removed

Post operatively with the first signs of tetany (numbness or tingling of the fingers positive Chvostek or Trousseau s signs) or with demonstrable hypocalcaemia calcium and vitamin D should be given orally For example 6 teaspoonfuls of calcium lactate and 100 000 units of vitamin D daily are generally adequate in cases where little or no bone disease has been found When the bones are extensively involved calcium by vein will generally be required as well For example 10% calcium gluconate may be given slowly with the first appearance of signs of tetany and followed by a slow drip containing 0 3% calcium gluconate As the bones improve and the serum alkaline phosphatase falls—the length of time required often a matter of weeks being proportional to the extent of the bone disease—it is important that the oral calcium and vitamin D be stopped before hypercalcaemia is produced

The treatment of osteitis fibrosa of renal failure is that of the kidney disease itself especially of the acidosis This and the complications it entails are dealt with in the chapter on kidney disease

The Differential Diagnosis of Metabolic Bone Diseases

It may be well to summarize the radiologic and chemical points which are of most value in the differentiation of the metabolic bone diseases

Radiologically the normal skull the normal lamina dura and the increased trabeculation found in osteoporosis the appearance and characteristic distribution of pseudo fractures in osteomalacia of *epiphyseal changes in rickets and of the typical kidney stones in renal* tubular acidosis and the presence of cysts in osteitis fibrosa are of the highest value In early osteomalacia however there may be no characteristic radiologic changes and in osteitis fibrosa recognizable cysts are often absent The osteitis fibrosa of renal failure may be impossible to differentiate radiologically from that of hyperparathyroidism

In most cases serum and urine chemical values will resolve the uncertainty Thus as regards the metabolic bone diseases a normal

alkaline phosphatase is found with osteoporosis alone and an elevated serum calcium with hyperparathyroidism alone Whereas the serum phosphorus is low both in osteomalacia and in hyperparathyroidism the serum calcium is virtually never high in the former, generally so in the latter

Renal failure is *frequently seen with hyperparathyroidism As this* results in retention of phosphorus and the serum calcium falls as the phosphorus rises there may come a point when one can no longer tell from the chemical findings whether the patient has primary renal failure or renal failure secondary to hyperparathyroidism Frequently there are no grounds upon which the distinction can be made The presence of band keratopathy (Cogan Albright and Bartter 1948) and of cortical cysts points strongly to primary hyperparathyroidism although their absence does not of course rule it out In any event, the distinction is in many cases an academic one since removal of a parathyroid adenoma *at this stage would be of little benefit and might produce tetany*

It is of interest to consider the extent to which two metabolic bone diseases can occur together Thus strictly speaking the compensatory increased bone matrix formation of osteomalacia and osteitis fibrosa could not occur in the presence of osteoporosis where the metabolic defect is precisely one of bone matrix formation

One might expect to find patients with the chemical findings of osteomalacia save for a normal alkaline phosphatase and the histological findings of osteoporosis It is likely that some cases of hunger osteopathy represent this combination of events (Wolff Eisner 1947 *Gsell* 1945)

Similarly in a patient with osteoporosis the bone destruction of osteitis fibrosa should be met with relatively little compensatory bone formation and less than the anticipated rise in the serum alkaline phosphatase This combination of events may explain the unusual severity of the bone disease often found with hyperparathyroidism in elderly or malnourished subjects

Finally osteomalacia might be superimposed *upon osteitis* fibrosa if there were in addition to the primary disease an increase in calcium loss sufficient to lower the solubility product in the serum below the critical value This condition which is rarely met with clinically, would presumably be self limited in that bone destruction would cease when osteoid seams covered all bone surfaces The slight increase in the width of osteoid seams (Fig 7) seen in all cases of osteitis fibrosa should not lead to a diagnosis of osteomalacia as well

Hypoparathyroidism

In *hypoparathyroidism* the serum phosphorus is elevated and the serum calcium lowered as a result of an insufficiency of parathyroid





FIG 1 (A) Normal vertebral bone (×3?) (B) Comparable section of bone from patient with severe osteoporosis (×3) Note decreased bone mass with otherwise normal structure in B

alkaline phosphatase is found with osteoporosis alone and an elevated serum calcium with hyperparathyroidism alone Whereas the serum phosphorus is low both in osteomalacia and in hyperparathyroidism the serum calcium is virtually never high in the former generally so in the latter

Renal failure is frequently seen with hyperparathyroidism As this results in retention of phosphorus and the serum calcium falls as the phosphorus rises there may come a point when one can no longer tell from the chemical findings whether the patient has primary renal failure or renal failure secondary to hyperparathyroidism Frequently there are no grounds upon which the distinction can be made The presence of band keratopathy (Cogan Albright and Bartter 1948) and of cortical cysts points strongly to primary hyperparathyroidism although their absence does not of course rule it out In any event the distinction is in many cases an academic one since removal of a parathyroid adenoma at this stage would be of little benefit and might produce tetany

It is of interest to consider the extent to which two metabolic bone diseases can occur together Thus strictly speaking the compensatory increased bone matrix formation of osteomalacia and osteitis fibrosa could not occur in the presence of osteoporosis where the metabolic defect is precisely one of bone matrix formation

One might expect to find patients with the *chemical findings* of osteomalacia save for a normal alkaline phosphatase and the histological findings of osteoporosis It is likely that some cases of hunger osteopathy represent this combination of events (Wolff Eisner 1947 Gsell 1945)

Similarly in a patient with osteoporosis the bone destruction of osteitis fibrosa should be met with relatively little compensatory bone formation and less than the anticipated rise in the serum alkaline phosphatase This combination of events may explain the unusual severity of the bone disease often found with hyperparathyroidism in elderly or malnourished subjects

Finally osteomalacia might be superimposed upon osteitis fibrosa if there were in addition to the primary disease an increase in calcium loss sufficient to lower the solubility product in the serum below the critical value This condition which is *rarely met with clinically* would presumably be self limited in that bone destruction would cease when osteoid seams covered all bone surfaces The slight increase in the width of osteoid seams (Fig 7) seen in all cases of osteitis fibrosa *should not* lead to a diagnosis of osteomalacia as well

Hypoparathyroidism

In hypoparathyroidism the serum phosphorus is elevated and the serum calcium lowered as a result of an insufficiency of parathyroid





FIG 1 (A) Normal vertebral bone (×37) (B) Comparable section of bone from patient with severe osteoporosis (×37) Note decreased bone mass with otherwise normal structure in B



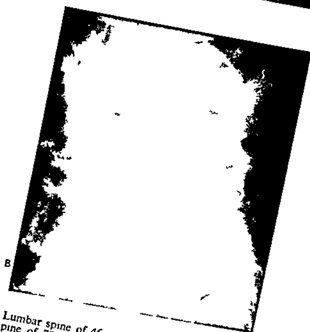


FIG 2 (A) Lumbar spine of 46-year old woman with Cushing's syndrome (B) Lumbar spine of 78 year old woman with post menopausal and senile osteoporosis Note columnar structure in A bowing of end plates and collapse of L 4 in B and radiolucency of bones in both

(Courtesy of Dr David Gould)



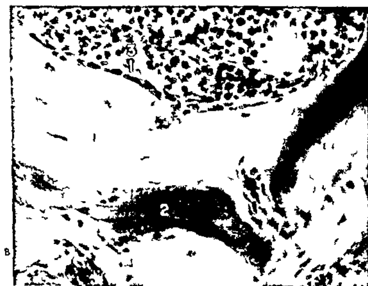


FIG 3 Vertebral bone from patient with osteomalacia or renal tubular acidosis A (×40) B (×3 5) Note increase of osteoid matrix (1) decrease in calcified bone (2) row of active osteoblasts (3) and absence of osteoclasts



FIG 4 Forearms of patient with osteomalacia (Milkman's syndrome) Note bilateral symmetrical fractures
(*Courtesy of Mrs Louis A Milkman*)

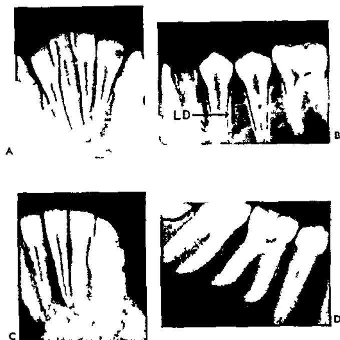


FIG 5 A and B normal teeth C and D teeth of patient with osteomalacia of renal tubular acidosis Note that lamina dura (LD) is absent in C and D
(*Courtesy of Dr Fuller Albright*)





Fig 6 Lower legs of two year old infant with r ckets of renal tubular ac dos s (A) Before intensive treatm nt (B) After five weeks of intensive treatment w th alkali and calc um Note prog ess e heal ng of r kets

(Co rt y of D David Go ll)



Fig 7 Tibial bone from patient with osteitis fibrosa cystica of primary hyperparathyroidism (×100) Note increase in osteoblasts (1) presence of osteoclasts (2) fibrosis of marrow (3) Osteoid is but slightly increased in width

(Courtesy of Dr Lent Johnson)



FIG 8 Hand of 43 year old woman with osteitis fibrosa cystica and renal failure A parathyroid adenoma was found at autopsy Note cortical cyst (1) and subperiosteal resorption of phalanges (inset)

(*Courtesy of Dr David Gould*)

hormone (A rise in renal tubular phosphate reabsorption will account for both these changes if it be assumed that the serum calcium falls as a solubility product for calcium phosphate is exceeded A decrease in the bone-destruction rate may also be a direct result of a deficiency of parathyroid hormone)

The most common cause of hypoparathyroidism is the excision of or damage to parathyroid tissue in the course of thyroid surgery This may be temporary—when the remaining tissue can undergo hyper trophy or the damaged tissue recover (a process often requiring weeks or months)—or permanent Rarely hypoparathyroidism appears without apparent cause Such idiopathic cases may appear as sequelae of acute infections and show for reasons not understood a predilection for children under 15 and adults over 40 (Drake Albright Bauer and Castleman 1939) An associated infection of the nails skin and mouth with monilia (candida) may be found in patients with hypoparathyroid ism and both diseases may be familial it is not clear which disease is primary (Sutphin Albright and McCune 1943)

Clinically the outstanding signs and symptoms in hypoparathyroidism are those of tetany which is of course a consequence of the hypo calcaemia These include numbness and tingling of the fingers and toes positive Chvostek and Trousseau signs laryngeal stridor muscle cramps and tonic muscular contractions Abdominal pains nausea and vomiting and generalized convulsions may occur In some but not all cases with convulsions it is apparent that an underlying epilepsy has been triggered by the tetanic state

As with hypocalcaemia of other causes premature cataracts are fre quently seen with hypoparathyroidism Other ectodermal tissues frequently show defects as well the roots and enamel organs of teeth developing after the onset of the disease may be hypoplastic the skin dry and scaly the head axillary and pubic hair scant

Calcifications within the basal ganglia often clearly apparent by X ray may furnish a valuable diagnostic clue Papilloedema and an increase of intracranial pressure are not infrequently observed When convulsions have been present with these findings a mistaken diagnosis of brain tumour has been made on a number of occasions

Histologically the bones are normal save in the rare cases (see below) with osteomalacia The parathyroid glands have been reported to show complete replacement by fat The low serum calcium the low or absent urinary calcium and the elevated serum phosphorus constitute the cardinal biochemical signs of hypoparathyroidism The serum alkaline phosphatase is generally normal

Two unusual biochemical findings in hypoparathyroidism are an *elevation* of urine calcium and an elevation of serum alkaline phos phatase The former often found with coccal urinary infection sug

gests a renal tubular defect the latter suggests that the ion product o calcium phosphate has not been maintained at a level sufficient for bone matrix calcification In such cases osteomalacia may be demonstrated

The differential diagnosis is that of tetany and of hypocalcaemia In alkalosis the elevated serum pH and the normal serum phosphorus and serum and urinary calcium clearly rule out hypoparathyroidism In rickets and osteomalacia hypocalcaemia is generally accompanied by a low serum phosphorus and virtually always by an elevated serum alkaline phosphatase In renal insufficiency, hyperphosphataemia and hypocalcaemia are frequently seen, and may suggest hypoparathyroidism Other signs of renal failure such as the elevation of non protein nitrogen in the blood and acidosis are generally present as well and there is seldom any real difficulty in differentiating the two conditions Should there remain any serious question between these two alternatives the response to parathyroid extract administered intravenously should provide a definitive answer Whereas in hypoparathyroidism a large phosphate diuresis (from 200 to 500 per cent of control excretion) follows within one to three hours after the extract is given little or no effect is observed in renal failure

The successful treatment of hypoparathyroidism should produce a lowering of the serum phosphorus and an elevation of the serum calcium The former may be accomplished by the elimination of milk and cheese from the diet and the use of aluminum hydroxide to increase the gastro intestinal loss of phosphate The latter may be accomplished by the use of calcium lactate gluconate or citrate orally together with vitamin D in dosages of 50 000 to 100 000 units a day Alternatively AT 10 (Hytakerol) may be given orally in doses of 1 cc (1 25 mg) to 3 cc a day It produces increases both in urinary phosphate loss and in calcium absorption The urinary calcium and if possible the serum calcium should be observed frequently while the therapy is being adjusted to avoid overdosage

Pseudo-hypoparathyroidism

A few cases have been described wherein the serum chemical abnormalities are those of hypoparathyroidism but the parathyroid glands are normal or hyperplastic and virtually no phosphate diuresis ensues upon administration of parathyroid extract This condition has been termed pseudo hypoparathyroidism and ascribed to a renal end-organ resistance to parathyroid hormone (Albright Burnett Smith and Parson 1942) (If the bones are also an end-organ upon which parathyroid hormone normally acts it must be assumed that they are also resistant to it in this condition They are normal histologically)

The signs and symptoms of pseudo hypoparathyroidism include those of hypoparathyroidism (save possibly for papilloedema) and include several characteristic developmental changes of diagnostic importance The subjects are almost all of short stature and many show a round face and are mentally retarded (Elrick *et al* 1950) In a number of them there is metaplastic bone formation in skin and fasciae Some metacarpal and metatarsal bones may be abnormally short as a result of premature epiphyseal closure and the corresponding fingers and toes appear short upon inspection The last two abnormalities suggest a relationship to myositis ossificans progressiva and achondroplasia Nothing is known of the fundamental cause of the disorder

It appears likely that the developmental abnormalities are genetically related to the metabolic ones but that they are not interdependent (Albright Forbes and Henneman 1952)

The treatment of pseudo hypoparathyroidism is the same as that of hypoparathyroidism If AT 10 is used longer doses may be required in the former condition

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CHAPTER 12

METABOLIC DISTURBANCES AND THE HAEMATOPOIETIC SYSTEM

R B THOMPSON

IN the first part of this chapter the metabolism of haemoglobin and of the principal substances known to be required for its synthesis is discussed The application of new techniques has greatly advanced our understanding of the metabolism of porphyrins and iron, so that these subjects are presented in some detail Since the isolation of vitamin B_1 and folic acid our knowledge of the megaloblastic anaemias resulting from deficiency of these substances has been greatly clarified and a brief summary of present views on this subject is included An increased interest in the influence of the endocrine glands on haemato poiesis has been stimulated by the discovery of cortisone and cortico trophin so that the final section is devoted to this subject The aim has been to correlate as far as possible the advances made in the laboratory with the clinical manifestations of disordered metabolism as observed at the bedside and to indicate any therapeutic applications

Haematologists have for so long been occupied with problems of morphology and nosology that the concept of haematopoiesis as a highly dynamic system is apt to be forgotten The haematopoietic organ —the bone marrow—roughly equals the liver in size weighing in the adult about 3 Kg normally only about one half of it is said to be in an active state Its function is to maintain the normal require ments of the body for erythrocytes granulocytes and platelets how this activity is controlled is not understood As the survival time of the granulocytes and platelets is not known with certainty the rate of production of these cells is not known it must however be very great Since the normal survival time of erythrocytes is known to be about 120 days and since the number of erythrocytes in the body can be estimated, the rate of production of erythrocytes can be calculated Taking the mean circulating blood volume of a 70-Kg man to be about 5 3 litres and the red-cell count as 5 0 mill per cu. mm of whole blood the total erythrocyte count of the body would be about 26 5 × 10 [illegible] It follows that 2 2 × 10 [illegible] erythrocytes must be produced by the marrow each day this number of red cells contains some 6 5 g of haemoglobin Since each gramme of haemoglobin contains 3 34 mg of iron about

22 mg of iron must be utilized daily and equivalent amounts of globin and porphyrin must be synthesized While these figures give some idea of the activity of normal marrow it is capable of very much greater production Studies of patients with congenital haemolytic (spherocytic) anaemia have shown that in an otherwise healthy patient the marrow can produce up to six times the normal number of red cells per day without anaemia appearing (Crosby and Ackeroyd 1952) It is useful to borrow the terms so commonly applied to other organs and ref r to compensated and decompensated haematopoiesis to this may be added the term dyshaematopoiesis which implies that the haematopoietic organ is diseased or deficient of necessary factors and cannot produce the normal requirements of the body Some of these factors requisite for normal haemoglobin synthesis and erythropoiesis are discussed in the following sections

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HAEMOGLOBIN METABOLISM

The haemoglobin molecule consists of four molecules of haem attached to one of the protein globin its molecular weight is about 68,000 Haem which is responsible for the characteristic colour of haemoglobin consists of one atom of iron in the centre of a molecule of protoporphyrin (Fig 3) Because of its great importance an account of iron metabolism is given first this is followed by a discussion of porphyrin synthesis Next follows an account of globin and of the remarkable series of variations of this protein which have become recognized in the last ten years

IRON METABOLISM

In the past our knowledge of the absorption and fate of ingested iron was derived from tedious balance experiments which were subject to considerable analytical errors More recently, many studies of iron metabolism have been made using tracer doses of radioactive iron This technique has made it possible to estimate iron absorption and excretion with greater accuracy to trace its transport in the plasma and its distribution in the body and to calculate the turnover between the various organs and tissues which utilize and store it By the use of the techniques now available the variations in the distribution and turnover of iron in disease are falling into fairly well defined patterns although our knowledge is by no means complete as yet

There are no entirely satisfactory estimations of the total body iron

in man but it is unlikely to exceed 4–5 g Using a rough estimate of 80 ml of whole blood per Kg body weight and since each ml of packed cells contains approximately 1 1 mg of iron the circulating red-cell mass of a 70-Kg man contains some 2 7 g of iron that is about 60 per cent of the total body iron Iron stores in the form of ferritin and haemosiderin amount to 1 2–1 5 g (Haskins Stevens Finch and Finch 1952 *Stevens Coleman and Finch* 1953) accounting for a further 30 per cent of the total Only about 3–5 per cent of the body iron is present as myoglobin and probably less than 1 per cent is contained in other haem enzymes concerned with oxygen transport in the tissues—cytochrome oxydase cytochromes b and c peroxidase and catalase

To assess the dietary requirements for iron we need to know the amount lost from the body and the proportion of dietary iron which is absorbed There is very strong evidence that the body controls its iron content by regulation of absorption by contrast with for example sodium and potassium which are freely absorbed but are very closely regulated in excretion This fact which is of fundamental importance to our understanding of iron metabolism was first clearly stated by McCance and Widdowson (1937) Only traces of iron are lost by way of the gastro intestinal tract (*Widdowson and McCance* 1937 McCance and Widdowson 1938 Maddock and Heath 1939 Copp and Greenberg 1946) Under normal circumstances urinary losses of iron are very small indeed After excessive intravenous doses of iron quite large amounts may transiently appear in the urine appreciable losses occur in paroxysmal nocturnal haemoglobinuria In men it is unlikely that the total daily loss exceeds 1 mg in women about 150–300 mg of iron are lost annually in the menstrual flow Losses in pregnancy total some 725 mg of this about 400 mg are transferred to the foetus 150 mg are lost with the placenta and 175 mg is accounted for by blood loss This represents an average deficit of some 2 7 mg a day during the pregnancy (Hynes 1948) At periods of bodily growth extra amounts of iron are also required Normal men must therefore absorb up to 1·0 mg daily and normal adult women up to 2 0 mg with an increase during pregnancy to approximately 3 7 mg

The most important dietary sources of iron are liver beef muscle eggs and dried fruits Moore and Dubach (1951) have shown by using foodstuffs labelled with radioactive iron that in normal human subjects only about 10 per cent of dietary iron is absorbed from the figures given above therefore it would appear that the generally recommended daily dietary intake of 12–15 mg is minimal There seems no doubt however that under conditions of iron depletion there is an increased absorption of iron in some early experiments Moore and Dubach (1951) were unable to demonstrate any increase in

iron absorption in patients suffering from iron deficiency anaemia later work by them however has reversed this conclusion (Moore and Dubach, 1955) Chronically anaemic dogs have been shown to absorb far more radioactive iron than do normal animals (Hahn Bale Ross Balfour and Whipple 1943) Hahn and his collaborators in 1951 showed that with a dose of not more than 9 mg of iron between the 15th and 25th weeks of pregnancy 35 per cent of ingested iron was absorbed and after the 35th week the figure rose to 40 per cent The patients studied by them were not anaemic, it may well be that anaemic women would absorb iron even more efficiently Balfour Hahn Bale Pommerencke and Whipple (1942) also found that absorption was increased during pregnancy to two to ten times that of non pregnant women

Apart from such variations in absorption to meet body requirements the conditions in the intestine have considerable influence on iron absorption It is retarded by a diet of high phosphate content which leads to the formation of insoluble iron phosphates Rats fed a very low phosphate diet on the other hand show excessive iron absorption (Kinney Hegsted and Finch 1949 Hegsted Finch and Kinney 1949) this observation is of interest in relation to the haemosiderosis seen in Bantus (see below) A high calcium intake diminishes the formation of insoluble iron phosphate but excessive calcium inhibits iron absorption (Anderson McDonough and Elvehjem 1940) That iron is more readily absorbed in the ferrous form (Moore Arrowsmith Welch and Minnich 1939) was confirmed by Moore, Dubach Minnich and Roberts (1944) using radioactive iron 1 5 to 15 times more ferrous than ferric iron was absorbed An acid medium is likely to enhance the amount of dietary iron which is available for absorption by converting iron hydroxide in foodstuffs to ferric ions and by reducing the formation of insoluble phosphates At an acid pH accessory factors act to convert the ferric to the ferrous form thus ascorbic acid cystein and the sulph hydryl groups of proteins could carry out such a reduction at a pH of 5 or lower Barer and Fowler (1937) found that patients with achlorhydria retain less iron from a normal dietary intake than do patients with free hydrochloric acid in the gastric juice With a large intake of iron (500 mg) the retention of iron was not influenced by gastric acidity such unphysiological amounts presumably swamp normal mechanisms and mask their effects Mettier and Minot (1931) demonstrated that suboptimal amounts of iron administered to patients with hypochromic anaemia gave better reticulocyte responses when the iron was in an acid medium In contrast to these observations Moore and Dubach (1951) fed radioactive iron (incorporated in eggs) by stomach tube at a pH of 1 5–1 8 to two patients with untreated hypo chromic anaemia At the end of one hour the pH of the gastric contents

was still below 2 0 absorption of Fe⁵⁹ was no greater than in a control period where the eggs were fed alone No effect on iron absorption was noted when aluminium hydroxide or sodium bicarbonate were added There seems no doubt however that in the normal subject with a normal dietary intake of iron gastric acidity has some influence on iron absorption Also certain is the common association of achlorhydria with iron deficiency anaemia in the development of such anaemia however other factors such as chronic blood loss and dietary deficiency usually clearly play a very important part In the usual therapeutic doses hydrochloric acid is unlikely to exert any significant influence on gastric acidity and is unlikely to be of any value in the treatment of the achlorhydric patient with iron deficiency anaemia

Ascorbic acid has long been known to enhance iron absorption (Powell 1944 Moore and Dubach 1955) It is always presumed to act by keeping iron in the reduced state in the intestinal lumen it could also upset the equilibrium in the mucosal cells and by increasing the concentration of reduced iron increase the amount transferred to the plasma There seems no doubt that many of the high figures which have been reported for percentage absorption of ingested iron can be explained by the simultaneous administration of ascorbic acid and ferrous iron

The most important site of iron absorption is probably the duodenum although it can be absorbed under experimental conditions from any area in the gastro intestinal tract (Hahn *et al* 1943 Endicott Gillman Breacher Ness Clarke and Adamik 1949 Stewart Yuile Claiborne Snowman and Whipple 1950) This may be of importance as a factor in the causation of iron deficienty anaemia after gastric operations Some unpublished evidence suggests that those patients in whom the duodenum is short-circuited are more likely to develop such an anaemia because of the malabsorption of iron than are others in whom the normal continuity is maintained

On reaching the mucosal cell the metal combines with an acceptor protein apoferritin to form ferritin the iron being in the ferric state Small amounts of ferrous iron are presumed to be present in the mucosal cells in equilibrium with the apoferritin and with the plasma iron When the apoferritin in the mucosal cells has combined to full capacity with iron from the intestine no more is absorbed until some has been passed on to the plasma the iron content of which presumably becomes lowered only with reduction of depot iron This is a very attractive theory but there are several pieces of evidence which it fails to explain For example patients with pernicious anaemia in relapse and patients with haemolytic anaemias may absorb quite large amounts of iron even though the plasma levels are high and there is clearly plenty of iron in the tissues (Dubach Callender and Moore 1948)

Rats rendered anaemic by phenylhydrazine were found to have more storage iron than normal animals, this could be accounted for only by an increased absorption of dietary iron (Stewart Vassar and Stone 1953 Kaldor 1954) In pyridoxine deficient swine there is elevation of plasma iron defective synthesis of haemoglobin, and the total body iron is elevated above normal yet absorption continues in these animals (Wintrobe, Follis Miller Stein Alcayaga Humphreys Suksta and Cartwright, 1944) In haemochromatosis too there is a breakdown of the controlling mechanism

Iron is transported in the blood stream by an iron binding protein which is probably a specific carrier each molecule can carry two atoms of iron in the ferric state This protein has been named transferrin or siderophilin it is a β_1 globulin (Cohn fraction IV—7) of molecular weight 90 000 The total iron binding capacity of serum is 240-300 μg/100 ml of serum but normally it is only one third saturated with iron The total iron binding capacity of serum can be measured it is increased in acute and chronic blood loss and in pregnancy and infective hepatitis In acute and chronic infections pernicious anaemia haemolytic anaemia cirrhosis uraemia and malignancy it is diminished Iron injected in excess of that which can be bound may well be responsible for some of the reactions observed with large intravenous iron dosage

The serum iron level is simply the sum of the amounts of iron being transferred between the various organs and tissues utilizing or storing it and that entering the body by absorption The values in normal subjects given by Powell (1944) were 143 μg /100 ml for men (S D 24) and 117 μg /100 ml for women (S D 26 5) Not all workers are agreed about this sex difference and others some using different methods have reported somewhat different figures Those given however fall within the commonly accepted range

The serum iron level is reduced in iron deficiency anaemia in infections (p 222) and during periods of active haematopoiesis It is elevated above normal in Addisonian pernicious anaemia in relapse in haemolytic and hypoplastic anaemias and as will be discussed in more detail below in haemochromatosis and allied disorders Hepatocellular damage also results in significant increases in serum iron level this *is especially marked during* the acute phase and falls with recovery it is not raised in early obstructive jaundice or in cirrhosis (Peterson 1952 Reissmann Boley Christianson and Delp 1954) It is probably released into the plasma from liver cells which have been destroyed There is evidence to suggest that the same thing happens with vitamin B_{12} (p 259)

Iron is probably passed from the transferrin of the plasma to tissue receptors it is most unlikely that transferrin itself enters the cells (Laurell 1951) There is no interchange of plasma iron with that

incorporated in the haemoglobin of mature circulating erythrocytes (Hahn Bale Ross Hettig and Whipple 1940)

Iron is stored partly as ferritin and partly as haemosiderin the latter is probably an aggregate of ferritin molecules and tends to appear with an increase in deposition of cellular iron above a certain point (Finch *et al* 1950 Gabrio Shoden and Finch 1953 Shoden Gabrio and Finch 1953) Haemosiderin is visible microscopically as golden brown granules whereas ferritin is not and it is stainable by iron stains which fail to demonstrate ferritin Iron can be readily mobilized from both ferritin and haemosiderin deposits unless these are unusually massive and have produced cell damage Even the haemosiderin in the liver in haemochromatosis can be utilized for haemoglobin synthesis if iron stores are depleted by phlebotomy (Finch *et al* 1950) A very convenient method of demonstrating haemosiderin in sternal puncture material by staining with the Prussian Blue reaction has been used to estimate iron stores In the normal subject small amounts are present there is a striking difference between men and women the latter having much less iron stored as haemosiderin In iron deficiency there is a virtual absence of marrow iron (Stevens *et al* 1953) and it has been shown that stores of haemosiderin and ferritin must be depleted before iron deficiency becomes manifest in the circulating red-cell mass The amount of iron stored by normal human subjects was estimated to be about 1200–1500 mg in a series of experiments where repeated weekly phlebotomies were carried out until iron deficiency became apparent in the peripheral blood (Haskins *et al* 1952) After these phlebotomies iron levels in the serum remained low for many months and one subject who was bled again a year later had practically no stores Iron reserves seem to be very slowly replaced after depletion stores were only very slightly increased by initial iron feeding six months of such feeding increased them by only about 200 mg

Probably in the normal the amount of iron leaving the plasma each day for haemoglobin synthesis averages 20 mg Extensive studies using radioactive iron of the turnover of iron in the body have been undertaken By means of surface counters it is possible to measure the amount of radio-iron taken up by various tissues and organs after administration by either the oral or parenteral route In disorders of haematopoiesis several patterns are described (Elmlinger Huff Tobias and Lawrence 1953) Excessive rates of iron turnover occur in anaemias where there is a shortened life span of red cells and an excessive production Low rates of turnover on the other hand occur in anaemias where there is aplasia or hypoplasia of the marrow whether from a primary disorder of the marrow itself or from a secondary involvement by leukaemia or other neoplastic cells or in myelosclerosis It is possible to differentiate splenomegaly with extramedullary haematopoiesis

from enlargements of the spleen from other causes and especially to distinguish those cases in which excessive destruction of erythrocytes is prominent A recent paper on the clinical application of this technique has been published by Wetherley Mein Hutt Langmead and Hill (1956)

When iron is administered to a patient with iron deficiency anaemia it is rapidly utilized for haemoglobin formation, indeed radio iron has been detected in haemoglobin as early as 4–8 hours after administration A response to iron is heralded by a reticulocyte peak, just as is the response of Addisonian pernicious anaemia to vitamin B_{12} The time of the peak and the duration of its rise are comparable—usually the peak is from the fifth to the tenth days and the rise lasts about 12 days The shape of the curve after iron is however often much flatter its height is in proportion to the severity of anaemia as measured by the haemoglobin level Wintrobe and Beebe (1933) observed a temporary increase in erythrocyte count to 6 million lasting sometimes for a month or two after iron therapy The red cell count may be above normal even when the haemoglobin level and the size and haemoglobin content of the red cells are still far from normal Even the haemoglobin reaches normal values before the MCV or MCH Thus the red cell count is not a safe guide in estimating the need for further treatment and even the haemoglobin level is not altogether reliable

After the reticulocyte peak the haemoglobin commences to rise this occurs at an average daily rate of 0 15 g but is very variable and may reach 0 25 g or be as little as 0 1 g /100 ml /day It does not seem possible to exceed this amount appreciably however the iron is administered, with adequate oral therapy the rise is almost as rapid as with parenteral iron administration The reticulocyte peak is however greater with parenteral iron It must be remembered that the anaemia must be corrected and then the body stores built up this takes time with oral therapy which should be continued for many months (Haskins *et al* 1952) An advantage of parenteral iron is the ease by which stores may be replaced by its use Tables are available for the calculation of dosage and many formulae have been devised Since the iron content of the haemoglobin of a 70-kg patient is about 2 7 g., a rough estimate of the iron deficiency can be made in any anaemic patient it will vary from about 0 3 to 2 0 g Adding to this the amount of iron required to replace stores—about 1 0–1 5 g —an estimate can be made of the amount of iron required in the therapeutic course

As has been mentioned above ascorbic acid will greatly enhance iron absorption there is no convincing evidence to indicate that any other substance should be added to oral iron preparations The responses in fact to plain inorganic iron preparations such as ferrous sulphate or gluconate alone are usually very satisfactory In a patient who is

not actually bleeding and who is suffering from a proven iron deficiency anaemia and who has undoubtedly been taking a potent oral iron preparation non response will usually imply an absorptive defect such as the sprue syndrome

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DISORDERS ASSOCIATED WITH ABNORMAL IRON METABOLISM

The Anaemia of Infection

The anaemia so commonly associated with infections and with many types of tissue damage receives very little attention in medical text books, patients suffering from this disorder moreover are commonly subjected to quite useless treatment by various haematinics because the nature of the underlying metabolic disturbance is unrecognized The subject has been very comprehensively reviewed recently

by Cartwright and Wintrobe (1952 and 1955) to whose work in this field much of our present knowledge is due

Anaemia is most commonly associated with chronic infections in the respiratory and genito urinary tracts it occurs also with osteo myelitis brucellosis and some fungal infections The location of the infective process and the type of infecting organism do not appear to be significant The anaemia so frequently associated with neoplastic diseases Hodgkin s disease collagen diseases trauma and burns and that which can be produced in laboratory animals by the injection of turpentine is characterized by very similar laboratory findings Al though the term anaemia of infection is clearly inadequate it is retained for convenience

Although excessive haemolysis may occur with some of the conditions mentioned above there is no increase of red cell breakdown in the true anaemia of infection Blood loss must of course be excluded A poor dietary intake of iron is likely in patients suffering from a chronic infective illness and impaired absorption may also occur however a slight microcytosis and hypochromia appear only in prolonged and severe cases It is of course quite common for an iron-deficiency anaemia or a megaloblastic anaemia to occur in a patient with one of the disorders mentioned above as causing the anaemia of infection In such patients the response to specific therapy will partly depend upon the activity of the underlying disease process A patient for instance with rheumatoid arthritis who is iron-deficient will often respond quite well to iron therapy although normal levels may not be reached until the underlying rheumatoid disease is in a quiescent phase

In the true anaemia of infection the anaemia is usually mild and is normochromic and normocytic The most striking change in iron metabolism is in the distribution of body iron a great concentration occurs in the liver and spleen A greatly increased turnover rate of radioactive iron in the liver has been well demonstrated in patients with rheumatoid arthritis by Elmlinger *et al* (1953) There is evidence that during infections the iron content of reticulo endothelial cells increases markedly It seems likely that this diverted iron plays an active part in the defence mechanism of the body against infection or in reparative processes but this role is not understood There is a reduction in the plasma iron level and in the iron binding capacity of the serum *the low transferrin levels are not however responsible for* the hypoferraemia (Cartwright and Wintrobe 1952) This hypo ferraemia so characteristic of the disorder is found early in infections frequently within 24 hours of the onset In mild cases hypoferraemia is often seen without anaemia with persisting infection the iron level remains low and anaemia may develop later As the anaemia subsides with resolution of the infective process the plasma iron level gradually

returns to normal The anaemia cannot be relieved by the administration of iron it responds only with recovery from the primary disease process During infection combative mechanisms appear to be of greater importance than the maintenance of normal erythrocyte levels but what determines this shift of priorities is unknown The free erythrocyte protoporphyrin (*q v*) has been found to be increased so that up to this stage haemoglobin synthesis appears to be unimpaired the observation may indicate a defect in the insertion of iron into the porphyrin molecule or a defective synthesis of globin

Polycythaemia

Polycythaemia vera is a condition characterized by a progressive and persistent elevation above normal of the total number of red cells in the circulation It is not solely a disorder of red cell production for elevated white cell counts and an increase of platelets are equally characteristic moreover there is a very definite tendency for patients to develop leukaemia The condition has recently been the subject of most valuable reviews by Lawrence Berlin and Huff (1953) and by Lawrence (1955) Polycythaemia vera must be carefully distinguished from polycythaemia secondary to cardiac or pulmonary disease or to living at high altitudes in which conditions white cell and platelet abnormalities are not found

In polycythaemia vera the total blood volume is elevated because of a high red cell volume the plasma volume is usually decreased As would be expected there is a very greatly increased turnover of iron but the values for this are often greater than those calculated on the assumption of a normal 120 day survival time for red cells This is explained by the presence of some abnormal red cells with a shortened survival time (Berlin Lawrence and Lee 1951) Whereas in normal persons about 20 mg of iron leaves the plasma daily for haemoglobin production in polycythaemia vera this daily turnover is always higher and may be as much as 200 mg In secondary polycythaemia on the other hand the iron turnover is about that expected with a normal 120-day survival time A further difference in the two disorders is apparent after oxygen administration for whereas in secondary polycythaemia this procedure depresses plasma iron turnover and iron uptake by red cells no such effect is produced in polycythaemia vera An interesting application of recently developed techniques is in the differentiation of certain cases of polycythaemia with very large spleens and usually very high white cell counts In some of these there is a very poor uptake of radioactive iron by the bone marrow and evidence of erythropoiesis in the spleen The marrow may show aplasia hypoplasia or fibrosis

In some cases elevated uric acid levels are found in one large series gout was found to be associated with polycythaemia vera in 10

per cent of patients (Videbaek 1950 see also Shelburne and Hanzal 1932 Tinney Polley Hall and Giffin 1945) A variety of polycythaemia has recently been described by Lawrence and Berlin (1952) which they call polycythaemia of stress It is usually seen in men in fourth and fifth decades there is usually hypertension and some of the patients had been subjected to undue nervous stress and strain These in dividuals have a low plasma volume but a normal total red-cell volume These cases seem to fit well with those described by Gaisbock (1922) and are often referred to by his name it is important that they be re cognized for the polycythaemia must not be treated by any of the measures used in polycythaemia vera

Disorders Associated with Excessive Amounts of Depot Iron

There are several disorders characterized by excessive iron deposition For the classical syndrome the name haemochromatosis is retained The term haemosiderosis is used for those cases secondary to multiple transfusions and to certain cases observed in the Bantu race It is also used for the excessive pigment so commonly found in haemolytic anaemias in the latter however the total quantity in the body does not usually approach that found in the other disorders The haemo siderosis which follows red cell breakdown is mainly concentrated in the reticulo endothelial system with intravascular haemolysis and after experimental injection of haemoglobin intravenously extensive deposits of haemosiderin occur in the renal tubules (Finch *et al* 1950) A recent review of experimental work on the deposition of iron in the tissues after administration of different forms of the metal has been published by Nissim (1953)

(1) **Haemochromatosis** As has been pointed out above the body can excrete only minute amounts of iron In haemochromatosis there fore the enormous deposits of between 25 and 50 g of iron found in the tissues must result from a breakdown of the mechanism by which the body normally so accurately controls iron intake If the disorder were congenital an absorption of an excess positive iron balance of only 1–2 5 mg a day would account for the deposits commonly found by the age of 50 The occurrence of occasional familial cases is certainly in favour of an inherited defect but the possibility that the abnormality can be acquired is certainly not excluded Radioactive iron studies (Dubach Callender and Moore 1948 Alper Savage and Bothwell 1951 Howard Balfour and Cullen 1954) have confirmed that there is indeed an increased absorption of iron some of the earlier denials of this were not warranted from the available evidence This increased absorption is the more remarkable as it occurs in spite of very high serum iron levels and almost complete saturation of the iron carrying protein So high are the serum iron levels and so great is the saturation

that estimations of these have great diagnostic value in the investigation of suspected cases (Houston and Thompson, 1952) Similar findings are obtained only in patients with transfusion haemosiderosis Pernicious anaemia in relapse and so called refractory anaemias are associated with raised serum iron levels but the iron binding protein is less saturated than in haemochromatosis Moreover diagnostic difficulty is unlikely to arise with these disorders As would be expected from the saturated state of the transferrin in haemochromatosis after a test dose of iron serum levels are characteristically flat and do not show the normal increase Presumably iron can be transferred only from the intestine to the plasma as fast as deposition of iron takes place in the tissues Extremely high serum iron levels have occasionally been reported in one instance a terminal value was 4020 μg /100 ml in another patient values of 7040 and 8000 μg /100 ml were obtained (Howard *et al* 1954)

Since the iron stored in the tissues is nearly all available for haematopoiesis it is possible to remove most of the deposits by repeated bleeding at weekly intervals the patient will not become anaemic until the stores are exhausted Disodium calcium versenate has been administered intravenously in an attempt to increase iron excretion in the urine Figueroa Adams Davis and Bassett (1955) conclude that while such treatment may be of value in secondary haemochromatosis it does not produce a great loss of iron and so is no substitute for phlebotomy in idiopathic haemochromatosis Further iron absorption can be retarded by giving oral phosphate 1 g of dicalcium phosphate with meals is recommended A very full account of all aspects of haemochromatosis has recently been published by Finch and Finch (1955)

(2) **Transfusion Haemosiderosis** This disorder was first described in 1937 by Kark in a patient who had received over 290 transfusions in nine years Since that time many more cases have been described and the disorder must be reckoned among the hazards of multiple blood transfusion About 250 mg of iron are contained in 500 ml of blood so that only transfusions of 100–200 pints are likely to lead to a deposition of iron comparable to the amounts found commonly in haemochromatosis Diabetes is rare in these patients though haemosiderosis and fibrosis were found in the pancreas in all of eleven cases examined (Schwartz and Blumenthal 1948) Skin changes are not common neither is the sexual hypoplasia so characteristic of haemochromatosis The time factor is no doubt of great importance in the development of the full picture of haemochromatosis those patients who receive the greatest number of transfusions over the longest time show the greatest degree of deposition of pigment and of tissue damage (Schwartz and Blumenthal 1948) The relationship of the deposition of pigment to the development of fibrosis though often assumed is not yet proved and

is still controversial The very striking male preponderance in all series of patients with haemochromatosis and due probably to the far greater iron losses in menstruation and in pregnancy in the female is not found in transfusion haemosiderosis

A patient with chronic haemolytic anaemia who developed the picture of haemochromatosis after prolonged oral iron therapy has been described (Wallerstein and Robbins 1953) he took approximately 1600 g of iron as a placebo over a twelve year period Analyses of the liver and spleen showed a total of over 15 g of iron which would represent an assimilation of about 3 per cent of the oral iron medication about 3 5 mg a day

The writer has seen one patient who was given nearly 15 g of intramuscular iron in error She presented with an intense brown pigmentation of the skin the serum iron was 145 μg /100 ml but this represented complete saturation of the iron binding protein There was no evidence of any visceral dysfunction

(3) Haemosiderosis in the Bantu Heavy deposits of iron in the viscera are very commonly found in the Bantu races of South Africa This disorder has been the subject of a recent study by Higginson Gerritsen and Walker (1953) They consider that excess dietary intake of iron is a possible explanation in these cases The Bantu diet is low in phosphate which is a possible contributory factor and it has been found in some instances that as much as 100–150 mg of iron may be ingested daily and is derived from cooking pots (Walker and Arvidsson 1950) Higginson and his co authors are impressed by the distribution of iron in their cases it seems more concentrated in the reticulo endothelial system than in the parenchyma of organs as in haemochromatosis The pancreas and heart are rarely involved and diabetes is very uncommon They do not think that there is any relationship between the deposition of pigment and the development of cirrhosis and fibrosis an opinion also held by Gillman and Gillman (1947) Cases are frequently seen where there is intense pigment deposition and yet no fibrosis The relationship which this disorder bears to haemochromatosis though often held to be close evidently requires further investigation

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COPPER METABOLISM

The daily requirement of the body for copper is about 2 mg this is readily supplied by even a very poor diet and no uncomplicated case of copper deficiency has ever been reported in man the subject has been summarized by Cartwright (1947) Moore (1945) gave anaemic children

copper sulphate two weeks after iron therapy and observed a second reticulocyte peak, it is therefore possible that copper may increase the haemopoietic response to iron therapy in children but this has never been demonstrated in adults and the addition of copper to iron preparations is quite unnecessary

It is known that in rats copper plays a part in the formation of cytochrome A cytochrome oxidase and catalase (Schultze and Kuiken 1941) Most of the copper in the plasma is bound to a globulin in the α_2 fraction known as coeruloplasmin It is thought unlikely that this is analogous to transferrin in that it is not involved in copper transport Hypercupraemia is found in infections (Cartwright and Wintrobe 1952) it is increased in the plasma in pregnancy but decreased in the plasma and whole blood and increased in the red cells in iron deficiency Recent knowledge of the subject is summarized by Cartwright (1950) There can be no doubt of the important metabolic role which it must play but the precise function of the copper so universally found in animal tissues is as yet unknown

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PORPHYRIN SYNTHESIS

The very large number of porphyrins synthesized in the laboratory by Fischer and his school proved the nature of the porphyrin nucleus and settled the configuration of the side chains It is only recently however that a series of fascinating studies has clarified our understanding of the processes whereby porphyrins are synthesized by living cells In many of these investigations isotopically labelled compounds suspected of taking part in porphyrin synthesis have been added to suspensions of living or lysed avian erythrocytes The porphyrins synthesized in these systems were then analysed for isotope content and the degree of incorporation of the various compounds was estimated As a result of such experiments the porphyrin molecule is now known to be synthesized by the condensation of glycine with a compound derived from succinate and α oxoglutarate The original experi

ments indicated that C^{14} labelled acetate was converted to a 4 carbon atom assymmetrical compound by way of the tricarboxylic acid cycle (Shemin and Wittenberg 1951, Shemin and Kumin 1952) Two molecules of a succinate intermediate were thought to condense with one molecule of glycine to form a porphyrin ring structure as indicated in Fig 1 More recently, isotopically labelled compounds have been

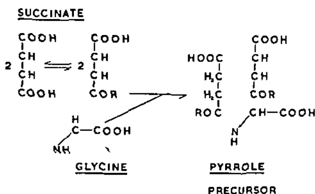


Fig 1 Hypothetical scheme of porphyrin synthesis

synthesized which are derivable from glycine condensed with one or two molecules of succinic acid to see if they were more readily incorporated into haemin than free glycine and succinic acid Shemin and Russell (1953) have shown that the incorporation of N^{15} and of C^{14} labelled aminolaevulinic acid into haemin is forty four times greater than that of labelled glycine The following account of a further series of experiments is taken from the recent paper by Neuberger and Scott (1953) it is illustrated in Fig 2 A carboxyl group of succinate may condense with glycine in two ways forming either succinamidoacetic acid (I) or α amino β oxoadipic acid (II) Compound (II) would readily decarboxylate to form δ aminolaevulinic acid (III) Either compound (I) or compound (III) could by addition of a second molecule of succinic acid be converted to δ succinamidolaevulinic acid (IV) By oxidative self condensation this compound might then form a pyrrole (V) Also compound (III) could condense to give a pyrrole with in addition an amino methyl substituent (VI) The first pyrrolic compound formed is probably (VI) and it is of great interest that a structure for porphobilinogen has recently been suggested which is identical with compound (VI) (Cookson Rimington and Kennard 1953 Cookson 1953) Furthermore evidence has been brought forward by Falk Dresel and Rimington (1953) that porphobilinogen when incubated with lysed avian red cells was converted to a mixture of porphyrins in 60% yield

It is apparent that the porphyrin formed by such a scheme would

have acetyl (CH COOH) and propyl (CH CH_2 COOH) side chains this is the configuration of uroporphyrin (Fig 3) By successive de carboxylations methyl (CH_3) and vinyl (CH CH) side chains are formed leading to copro and proto porphyrin This hypothesis has not yet been proved uncertainty still exists about the relationship of coproporphyrin it probably is a true intermediate but some consider

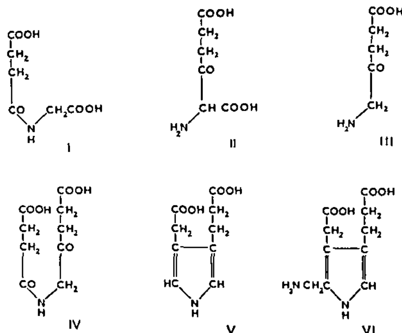
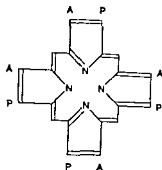


FIG Illustrates the synthesis of the porphyrin ring according to Neuberger and Scott (1953) I Succinamidoacetic acid II amino-β-oxoadipic acid III δ aminolaevulinic acid IV δ succinamidolaevulinic acid Compounds V and VI are hypothetical porphyrin precursors compound VI probably identical with porphobilinogen

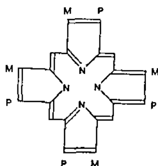
it more likely to be a by product The function of the propyl groups appears to be in the orientation of the haem molecule and its attachment to globin The vinyl groups seem to be necessary for the incorporation of iron into the ring the methyl groups are presumed to be inert they act as a protection and render the ring more stable

Fischer recognized in 1930 that there were four possible porphyrin isomers in nature only types I and III are found As can be seen from Fig 3 the difference lies in the arrangement of the side chains in type I porphyrins these are symmetrical but in the type III isomers to which the porphyrin of haem belongs the order is asymmetrical so that the two propyl groups are adjacent It is impossible to derive one type of

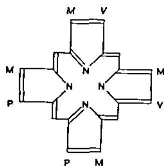
UROPORPHYRIN III



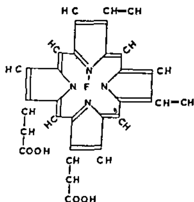
COPROPORPHYRIN III



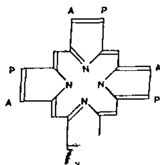
PROTOPORPHYRIN III



HAEM



UROPORPHYRIN I



COPROPORPHYRIN I

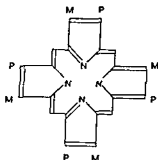


FIG 3 Il re of precursors uroporphyrin, copro-
porphyrin of with the structure of the related
compounds ur In the above figure A = acetyl
CH_2—COOH H_3 H P = propyl CH_2—CH
H

porphyrin from the other The reason for the occurrence of only these two isomers has been the subject of much conjecture the order in which pyrrole rings are linked and the arrangement of the amino methyl substituents (Fig 2 VI) in the condensation process to form the methene bridges are probably the controlling factors

Erythrocyte Porphyrins

Circulating erythrocytes contain coproporphyrin (ECP) and proto porphyrin (EP) in the free form uroporphyrin has not as yet been demonstrated in erythrocytes These findings correlate with the demon stration of fluorescytes by Seggel (1940) which are red cells exhibiting fluorescence in ultraviolet no doubt due to the presence of free por phyrins The EP is nearly all of the III isomer the amounts of ECP present correlate extremely well with the reticulocyte count The normal range of ECP values is 0–2 0 μg /100 ml of erythrocytes the mean value for EP is about 30 μg /100 ml (Watson 1950 1951) In Table I

TABLE I

Disorder	*Erythrocyte Protoporphyrin (EP)*	*Erythrocyte Coproporphyrin (ECP)*
Iron deficiency	Very great increase	Normal or slight increase
Infections	Great increase	Normal or low
Lead poisoning	Great and maybe enormous increase	Great increase
Haemolytic anaemia	Moderate increase	Great increase
Pernicious anaemia		
Relapse	Low normal	Not demonstrable
On treatment	Rises but later than EC	Early sharp rise with slight lag behind and close correlation with reticulocytes

the variations in these values in certain blood disorders are given In iron deficiency porphyrin synthesis is normal and the red cells are filled by protoporphyrin which has no available iron for its conversion into haem This finding is evidence in favour of the concept that haem and globin are formed as separate entities before combining In the anaemia of infection the findings are similar except that the proto porphyrin values are not so high As is stated on page 224 it is thought that in the anaemia of infection there is interference with the insertion of iron into the porphyrin ring though there may possibly be a defect of globin synthesis In both iron deficiency and infection the copro

porphyrins are low presumably there is no interference with the decarboxylating mechanism responsible for their conversion into protoporphyrin In lead poisoning the findings are of great interest There is at times an enormous increase in EP values and these are always greatly raised There is also a great increase in ECP it will be recalled that coproporphyrin III also appears in the urine The present concept is that lead interferes with the conversion of copro to proto porphyrin and probably also with the formation of haem The above findings and other facts (Watson 1936) strongly suggest that the major role in the production of the anaemia of lead poisoning is played by inhibition of haem synthesis Any severe degree of haemolysis is exceptionally rare in chronic lead poisoning the writer is unaware of any detailed studies of red cell survival Certainly in acute lead poison ing—as in patients treated with lead for malignant disease—there was evidence of actual damage to the erythrocytes and it is probable that the erythrocytes of chronic lead poisoning are also damaged and pre maturely removed from the circulation That haemolysis is in part responsible for the anaemia of lead poisoning is suggested by the animal experiments of Baikie (1954)

In haemolytic anaemias the findings at first sight suggest a block in the formation of proto from copro porphyrin but it seems probable that the red cells are formed and discharged into the circulation too rapidly for full synthesis to occur In pernicious anaemia in relapse haemoglobin formation may well have time to proceed fully before *the nucleated haemoglobinated precursors lose their nuclei* and the cells are released into the circulation This is conceivable even after considering the increased rate of destruction so commonly found in pernicious anaemia in relapse After treatment the ECP rises sharply with a slight lag behind the reticulocyte count later still the EP also rises

Abnormal Porphyrin Metabolism

Abnormalities of porphyrin metabolism are usually separated into the porphyrinurias and the porphyrias The former comprise those cases where abnormal amounts of porphyrin are excreted in association with various disorders such as poisoning by lead and other heavy metals diseases of the liver, anaemias and infections The porphyrias are a group of metabolic disorders probably all congenital, though often not becoming manifest until later in life It is unfortunate that the nomenclature of porphyrins is so confusing The name coproporphyrin was given to a porphyrin first isolated from faeces uroporphyrin was first recovered from the urine Protoporphyrin was originally assumed to be the parent substance for it was not realized that porphyrins are precursors and not breakdown products of haem The term haemato

porphyrin is still wrongfully applied in clinical text books to the mixture of porphyrins occurring in the urine in acute porphyria

Porphyrinuria

Here excessive porphyrin excretion occurs but there is no primary disorder of porphyrin metabolism as in the porphyrias and the amount of porphyrin excreted is far smaller The abnormal amounts of porphyrin do not as far as is known give rise to any symptoms such as are so characteristic of the porphyrias

Excessive excretion of coproporphyrin III occurs in poisoning by chemicals and heavy metals such as lead It is also found during the course of aplastic anaemias and those anaemias loosely called refractory This finding offers some support for the suggestion that many of these aplastic states are a result of chemical poisoning of the marrow Under conditions of increased erythropoiesis there is increased excretion of type I porphyrins it is presumed that these are by products of the increased isomer III production Porphyrinuria occurs commonly in cirrhosis of the liver Some very interesting recent findings are discussed by Watson (1951) who has shown that in non alcoholic cirrhosis and in haemochromatosis there is excretion of type I isomer whereas type III is found in alcoholics and persists for long periods in those with cirrhosis On both obstructive jaundice and infective hepatitis type I isomer is found The excessive type III excretion in Hodgkin s disease and in poliomyelitis is as yet unexplained

A discussion of porphyria is given in Chapter 13 p 328

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GLOBIN

Globin is a protein with a molecular weight of about 66 000 Unusually large amounts of histidine are present in the molecule This is largely responsible for the basic character of globin The imidazole groups of histidine are probably of great importance in the linkage of globin with the iron atoms of haem the precise nature of the haem globin bonding is not as yet fully understood

Intense protein synthesis is known to occur in the basophilic nucleated red cell precursors of the bone marrow and it is assumed that these cells are the site of globin production It has been clearly shown in laboratory animals that protein starvation produces an anaemia which is reversible after protein feeding (Cartwright, 1947) Defective globin synthesis may occur in certain anaemias of malnutrition but this has never been proved it is also a remote possibility in the anaemia of infection (*q v*)

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CONGENITAL ABNORMALITIES OF HAEMOGLOBIN INVOLVING THE GLOBIN MOIETY

It has been known for many years that there are differences in chemical and physical properties between the predominant haemoglobin of the foetus (haemoglobin F) and that found in the normal adult (haemoglobin A) these differences are reviewed in some detail by White and Beaven (1954) In haemoglobins F and A (as well as in other variants to be discussed below) the haem moiety is identical only the globin differs Haemoglobin F can be distinguished most conveniently from haemoglobin A by means of its very much greater resistance to denaturation by alkali (Singer Chernoff and Singer 1951) Using this technique it can be demonstrated that foetal haemoglobin predominates during intra uterine life and at birth comprises from 55 to 98% of the total haemoglobin Three to four months after birth it is greatly reduced but it can be detected until the end of the second year in normal individuals In a group of disorders of the blood forming organs in adult patients small amounts of foetal haemoglobin were found by Singer *et al* (1951)

The alkali denaturation test is relatively crude however and more

recently it has been found by using a more delicate quantitative precipitin test that over 50% of normal adult bloods contain remarkably constant amounts of foetal haemoglobin (Chernoff 1953) Usually there is less than 0 1 % present but occasionally 1 0% may be found To detect such minute amounts of foetal haemoglobin with certainty a very high degree of purity of immunizing and test antigen is essential When this more refined technique was used increased amounts of foetal haemoglobin were found during the second trimester of pregnancy in ten out of ninety one patients studied by Rucknagel and Chernoff (1955) Later in pregnancy these amounts decreased no increase was demonstrated after delivery The authors conclude that the foetal haemoglobin was produced by the mother as a response to the stress of early pregnancy just as foetal haemoglobin appears in increased amounts in certain blood diseases It seems very improbable that the foetal blood could be accounted for by transplacental transfer The method was not sensitive enough to detect such minute amounts of foetal blood as it is postulated may be transferred across the placenta and result in Rh sensitization Amounts of foetal blood exceeding 10 ml would however have been detected

The electrophoretic mobility of foetal haemoglobin lies between that of adult haemoglobin and sickle cell haemoglobin (see below) so that it is difficult to distinguish a small foetal component in mixtures of the other two by this technique More recent methods employing ion exchange chromatography have however succeeded in obtaining good separation of foetal and adult haemoglobins as well as other varieties (Prins and Huisman 1955)

Amino acid estimations have been made by chromatography within the last few years and it has been shown that the most striking differences are in the higher amounts of serine and isoleucine and lower amounts of valine in foetal as compared with adult haemoglobin (Schroeder Kay and Wells 1950 and Van der Schaaf and Huisman 1955) By this technique the presence of traces of foetal haemoglobin (0 3–0 4 %) was confirmed in the blood of normal adults (Huisman Jonxis and Dozy 1955a)

Apart from the conditions discussed above haemoglobin F is found most prominently in certain inherited disorders either with haemoglobin A or with some other pathological haemoglobin Chernoff (1953) by immunological methods has shown that the alkali resistant haemoglobin in these inherited haemoglobinopathies is identical with that produced by the normal foetus

In both forms of Mediterranean anaemia (thalassaemia major or Cooley s anaemia and thalassaemia minor) haemoglobins A and F are found In the minor form only a small proportion of F occurs but in the major variety it may comprise 40–100% of the total It is

probable that in the minor form only one gene is present but in thalassaemia major two genes occur, if the parents of a major case are examined carefully both will be found to carry the trait (Neel and Valentine 1947) It has been suggested that the thalassaemia gene produces its effect by inhibiting the production of haemoglobin A (Rich 1952)

Hollingsworth (1955) has shown that foetal erythrocytes obtained from the umbilical cord at birth (containing 54–64% of foetal haemoglobin) had a short life span when tagged with radioactive sodium chromate and transfused to normal adult recipients This might suggest that the haemolytic syndrome in thalassaemia was due in some way to the presence of foetal haemoglobin Again since the major form (Cooley s anaemia) is associated with a severe haemolytic syndrome and the minor form is a much more benign disorder it might seem reasonable to associate severity of the disease with the amount of foetal pigment present Studies of this question have however failed to show any correlation (Minnich, Na Nakorn Chongchareonsuk and Kochaseni 1954 Smith Schulman Ando and Stern 1955)

As will be pointed out in the following discussion a haemoglobinopathy in the homozygous condition is usually associated with a haemolytic syndrome the heterozygous condition being benign It seems very probable that in the homozygous state other abnormalities of the erythrocyte are present perhaps there is some defect of the stroma

Studies in which normal erythrocytes were transfused into cases of Cooley s anaemia have given varying results These difficulties seem to be resolved by the recent work of Smith *et al* (1955) who point out that a normal cell survival time of transfused normal erythrocytes is to be expected in infants suffering from the disease but that a decreased survival time is to be expected in children and young adults An increased life span of transfused normal erythrocytes occurred in such cases after splenectomy There is therefore evidence of a haemolytic factor as well as of a haemoglobin abnormality There is probably also a block in haemoglobin synthesis (Dacie 1954) The pathological findings have often been remarked upon as unusual for an uncomplicated haemolytic anaemia (Wintrobe 1951) The serum iron for instance is high as it would be in a haemolytic anaemia but the iron binding protein is saturated as in haemochromatosis Again the deposits of pigment follow a pattern resembling that seen in haemochromatosis It seems probable that there are several genetic defects present to account for all the observed abnormalities in thalassaemia Hoffman Wolman Hillier and Parpat (1956) have demonstrated abnormal erythrocyte membranes in thalassaemia major

In the course of investigations into the phenomena of sickling of erythrocytes it was discovered that in sickle cell anaemia a variant of

haemoglobin (designated haemoglobin S) was present which could be separated electrophoretically from haemoglobins A and F (Pauling Itano Singer and Wells 1949) With rare exceptions it is limited to the Negro race As in thalassaemia there are two forms of the disorder sickle-cell trait and sickle-cell disease The latter is the severer form and here both parents have the trait one in four of the children will have two sickle-cell genes and will develop the disease In the trait haemo globins A and S are found but in the disease the combination is of F and S Singer and Singer (1953) have demonstrated that the pheno menon of sickling is associated with gelation of haemoglobin S long thin boat shaped particles or tactoids being formed which are thought to be responsible for the very characteristic shape of sickled cells (Harris 1950) No direct correlation has been demonstrated between the absolute amounts of haemoglobins S and F and the clinical severity of cases of sickle-cell anaemia This has been explained by Singer and Fisher (1952) who have demonstrated that the red cell population in patients with sickle-cell anaemia seems to be composed of three fractions in one the cells contain mainly haemoglobin S in another the S and F pigments are mixed and in the third the majority of the haemoglobin is of the F type Much interest has been aroused by recent descriptions of combined genetic defects one of these is sickle cell thalassaemia disease the individual having inherited one abnormal gene from each parent A recent description of this combination has been published by Singer Singer and Goldberg (1955) References to combinations of sickle cell and other genes are made below

Yet another variant is haemoglobin C which can be readily differ entiated from haemoglobins A and S by its greater electrophoretic mobility Huisman van der Schaaf and van der Sar (1955b) have re ported that it contains a larger number of lysine and perhaps histidine residues than do haemoglobins A S and F As with other haemoglobin abnormalities it may occur in a homozygous form one abnormal gene for haemoglobin C having been derived from each parent or in a heterozygous form where only one haemoglobin C gene is present the other being for normal haemoglobin A Some very interesting indi viduals have recently been described in whom a haemoglobin C gene has been associated with one for thalassaemia (Zuelzer and Kaplan 1954 Singer Kraus Singer Rubinstein and Goldberg 1954) The gene may also be associated with that for haemoglobin S producing sickle cell haemoglobin C disease (Neel Kaplan and Zuelzer 1953 Kaplan Zuelzer and Neel 1953)

The combination of haemoglobins A and C in the heterozygous condition produces an asymptomatic carrier state—the haemoglobin C trait Homozygous haemoglobin C disease was first described by Spaet Alway and Ward (1953) further accounts have been given by Singer

Chapman Goldberg Rubinstein and Rosenblum (1954) and by Wheby Thorup and Leavell (1956) To date it has been described only in the Negro race A benign and well-compensated haemolytic syndrome is usually described A striking feature is the high percentage of target cells (30–100%) these are also found though in much smaller numbers in other conditions where haemoglobin C is present As not all red cells containing haemoglobin C are target cells it seems very likely that some other factor affecting the stroma is responsible As would be expected from this appearance there is a markedly increased osmotic resistance to saline As only moderate reticulocytesis is usual spleno megaly may be marked Splenectomy does not appear to have any effect on the haemolytic process it may be indicated if there are severe pressure symptoms or if there is evidence of hypersplenism with throm bocytopenia and leukopenia

Haemoglobin D was first discovered in a family of English Irish and American Indian origin by Itano (1951) This variant has the same electrophoretic mobility as haemoglobin S but can be distinguished by a greater solubility in the reduced state it does not cause sickling Unlike haemoglobin S and C it seems to have a remarkably wide racial occurrence cases have been described in African Negroes American Indians Algerians Turks and in North west Indians

Sturgeon Itano and Bergren (1955) have described cases in whom haemoglobins S and D have occurred together there was a mild anae mia and a haemolytic process The clinical features of homozygous haemoglobin D disease are not known

Haemoglobin E was found in a child with an atypical anaemia (Itano Bergren and Sturgeon 1954) It is found mainly in South east Asian races and is associated with a mild haemolytic syndrome (Chernoff Minnich and Chongchareonsuk 1954 Lehmann Story and Them 1956) It has an electrophoretic mobility greater than that of haemoglobin A and slightly less than haemoglobin S Its amino acid composition appears to be the same as that of haemoglobin A (Jonxis Huisman van der Schaaf and Prins 1956)

Haemoglobin G was reported by Edington and Lehmann (1954) and by Edington Lehmann and Schneider (1955) Haemoglobin H was found in one Chinese family the clinical manifestations were those of thalassaemia major (Rigas Koler and Osgood 1955) Haemoglobin I also has as yet been described in only one family Six of seventeen members of a Negro family were affected but no haematological abnormalities were observed (Rucknagel Page and Jensen 1955) Two additional haemoblogins have recently been described in Liberia (Robinson Zuelzer Neel Livingstone and Miller 1956) The subject of abnormal haemoglobins has been very fully reviewed by Itano Bergren and Sturgeon (1956)

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SOME ABNORMALITIES OF HAEMOGLOBIN INVOLVING HAEM

Methaemoglobin When functioning in oxygen transport reduced haemoglobin forms a covalent compound with oxygen A true oxidation can also take place however the iron in haemoglobin being converted to the ferric from the normal ferrous state this ferric haemoglobin is commonly known as methaemoglobin though Lemberg and Legge (1949) prefer the name haemiglobin as being more rational The oxidation is readily reversible it is indeed probable that constant oxidation and reduction occur in normal erythrocytes, Heubner s

(1940) figure of 1 7% of methaemoglobin in normal blood is generally accepted It has been suggested that as much as 0 5 g of methaemoglobin is reduced per hour per 100 ml of erythrocytes under normal conditions (Eder Finch and McKee 1949) Ascorbic acid is present in red cells and on oral administration can reduce the cyanosis of congenital methaemoglobinaemia glutathione has also been demonstrated in erythrocytes but what part if any these substances play under normal conditions is unknown The most important physiological mechanism probably involves co enzyme I and depends on the breakdown of glucose interference at the triosephosphate dehydrogenase stage by substances such as fluoride and iodoacetate which inhibit glucolysis can retard the process of reduction

Solutions of methaemoglobin are brown The absorption spectrum has four bands that in the red at 633 μ being the most important for indentification this band disappears on adding sodium cyanide or hydrosulphite Methaemoglobin may be readily produced in the laboratory by the action of potassium ferricyanide on any haemoglobin derivative It is not always easily demonstrated dilutions of blood in distilled water from 1 5 to 1 20 should be examined in a strong light

Clinically methaemoglobinaemia is commonly associated with poisoning by certain compounds among which are the following chlorate and nitrite bismuth subnitrate ammonium nitrate organic nitrites aromatic nitro and amino compounds such as aniline and nitrobenzene Many drugs in common use may produce it—phenazone methyl sulphonal and sulphonal phenacetin acetanilide acetylsalicylic acid and some sulphonamides (sulphanilamide sulphapyridine and sulphathiazole in this order of activity) Methaemoglobinaemia after contact with freshly dyed garments and with unlaundered napkins stamped with aniline dyes has been reported Numerous examples are recorded in infants from ingestion of excessive amounts of nitrite in well water Absorption of nitrites from the intestine has been held responsible for cases of enterogenous cyanosis in such patients there is usually a combination of meth and sulph haemoglobin By what mechanism many of these substances produce methaemoglobin is not understood Nitrophenols are known to inhibit cytochrome reductase and it may well be that many of these compounds act by an inhibition of the normal reduction enzymes present in erythrocytes Cox and Wendel (1942) produced methaemoglobinaemia in dogs by administration of aniline and nitrobenzene They studied the rate of disappearance of methaemoglobin from the blood of these animals *in vitro* and concluded that increased formation of methaemoglobin and not an inhibition of reduction was occurring This matter evidently requires further investigation

As many of the substances which can produce methaemoglobinaemia

may also produce haemolysis it is not surprising that some patients have an associated haemolytic anaemia an outstanding example of *such a substance* is phenylhydrazine This and—among others—aniline compounds may damage the red cell in other ways and Heinz Ehrlich inclusion bodies which are probably denatured globin may be found

Apart from the cases due to poisoning mentioned above there are some forty cases of congenital methaemoglobinaemia reported in the literature Several members of a family may be affected, one family of eighty five members in five generations which included ten children who were cyanotic at birth is recorded (Codounis 1952) In some instances there seems to be a recessive in others a dominant inheritance Cyanosis is usually present from birth It seems very probable that there is a congenital deficiency of the normal reducing system Confirmatory evidence of this has been published by Breakey, Gibson and Harrison (1950) who have demonstrated a deficiency of co-enzyme I in the erythrocytes It is suggested that in the presence of methylene blue which is very effective in reducing the cyanosis the normally much less efficient system involving co-enzyme II is able to reduce the methaemoglobin Barcroft Gibson Harrison and Mc Murray (1945) have demonstrated a deficiency in a co enzyme factor probably a flavoprotein which mediates between co-enzyme I and methaemoglobin Flavine adenine dinucleotide has however been found in the red cells in normal amounts by Eder *et al* (1949) A recent review of these complex metabolic processes occurring in the erythrocytes has been published by Prankerd (1955)

The action of methylene blue *in diminishing the cyanosis* seems at first sight paradoxical for it can itself produce methaemoglobin it is not however very efficient the reducing action being more effective Bodansky (1950) suggests that reduced diphosphopyridine nucleotide *interacts with methylene blue to form diphosphopyridine* nucleotide and leukomethylene blue the latter then reacts with methaemoglobin to give haemoglobin and methylene blue Presumably ascorbic acid acts by enhancing reducing mechanisms in the erythrocyte, however it *is not nearly so effective a reducer as methylene blue*

Methaemoglobin does not combine with oxygen and so has no respiratory function - presence shifts curve of oxyhaemoglobin very similar dane effect of carbon monoxid R tissue anoxia which results ith quite low obin concentrations The dom is c is most readily mucc and ls Clubbing is not as by red of a blue may

mental confusion and general weakness but they are usually much more blue than sick The disorder has been described in a family in association with mental deficiency and neurological abnormalities (Worster Drought White and Sargent 1953)

Treatment of the congenital variety is by ascorbic acid in doses of 100–500 mg a day by mouth Methylene blue is also effective the dose is 100–300 mg by mouth In the acquired variety ascorbic acid works too slowly to be of any value but oral methylene blue or 1 mg /Kg intravenously is very effective

Sulphaemoglobin This pigment contains one more sulphur atom than haemoglobin Where in the haemoglobin molecule this sulphur is attached is uncertain it seems likely however that it is placed in the iron iminazole nitrogen linkage normally present between haem and the globin molecule Unlike methaemoglobin it is not possible to reduce sulphaemoglobin to haemoglobin the compound does not alter the life span of the erythrocyte containing it and so remains *in situ* until the dissolution of the cell comes about This fact has been utilized as a means of estimating the normal life span of erythrocytes It is an intracellular pigment only in very severe cases where there is a haemolytic agent also present as in clostridum welchii septicaemia is sulphaemoglobin ever detectable in the plasma

Sulphaemoglobin is produced by very similar agents to those responsible for the appearance of methaemoglobin it is therefore not surprising that the two pigments are often found together Acetanilide phenacetin and some sulphonamides are common causative agents Sulphur itself sulphides and thiosulphate can produce it directly Hydrogen sulphide produced by excessive bacterial fermentation in the intestine is responsible for its formation together with methaemoglobin in cases of enterogenous cyanosis Morgan and Anderson (1940) demonstrated that oxidation products of aniline compounds—phenyl hydroxylamines and *p* aminophenols—when added to blood lead to the rapid formation of sulphaemoglobin if a trace of sulphide is present and of methaemoglobin if sulphide is absent

Sulphaemoglobin does not combine reversibly with oxygen and hence has no respiratory function it can be oxidized the ferrous iron becoming ferric as in the oxidation of haemoglobin to methaemoglobin It is not easy to distinguish sulphaemoglobin from methaemoglobin by spectroscopy methaemalbumen too has a similar spectrum but is found only in the plasma The band of sulphaemoglobin at 620 μ persists after treatment with cyanide or excess of 1% sodium carbonate but these reagents cause a disappearance of the nearby methaemoglobin band at 630 μ

The symptoms are very similar to those of methaemoglobinaemia Administration of reducing agents is of course of no value

Methaemalbumin This pigment was originally described by Fairley (1941) in blackwater fever it is also found in other cases of severe haemolysis in severe liver disease and in small amounts in some cases of Addisonian megaloblastic anaemia It consists of the ferric complex of protoporphyrin known as haematin bound to albumin As was pointed out above it is found in the plasma and not in the red cells

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ANAEMIA ASSOCIATED WITH HEPATIC AND RENAL DISEASE

The Anaemia of Liver Disease

That anaemia occurs in association with cirrhosis of the liver is well recognized and yet if we exclude those cases in which it follows acute or chronic blood loss the cause is very poorly understood The macrocytic type has caused the greatest interest and will be discussed here it occurred in 20 of Jarrold and Vilter s (1949) 30 cases of cirrhosis there were in addition 4 patients with normochromic anaemia 6 were not anaemic The presence of anaemia can usually be detected by ordinary methods but as Hyde Berlin Parsons Lawrence and Port (1952) have pointed out in their study of blood volumes in cirrhosis the haematocrit value may be misleading since there may be a normal low or high red-cell volume and the total blood volume may be

normal or low These volume changes could not be correlated with the physical findings or with laboratory tests of hepatic function The peripheral blood picture is usually one of moderate macrocytosis anisocytosis poikilocytosis and polchromasia are minimal The hyper segmented macropolycytes of vitamin B_{12} and folic acid deficiency are not seen A slight rise of reticulocytes is sometimes found in the absence of recent haemorrhage a finding which would suggest a haemolytic process The bone marrow though sometimes of poor cellularity is often normally cellular There may especially in cases of more severe anaemia be a marked normoblastic hyperplasia with many macro normoblasts precursors of the peripheral macrocytes Many early forms of erythroblasts may be found and cause confusion with megalo blastic erythropoiesis The nuclear chromatin of these cells is however much more densely clumped than that of megaloblasts and the over all picture is usually clearly one of normoblastic hyperplasia Jarrold and Vilter (1949) comment on the number of plasmacytes often found in bone marrow smears from cirrhotic patients they correlate this with *hyperglobinaemia and suggest a causal relationship*

There are a few reports of megaloblastic erythropoiesis in cirrhosis three of Jarrold and Vilter s patients showed such changes and others have been described by Movitt (1949 and 1950) It seems clear that in these cases there was an associated nutritional deficiency megaloblastic anaemia possibly due to lack of extrinsic factor (vitamin B_{12}) from the diet Response to specific treatment in these patients has been poor It must be remembered here that Addisonian pernicious anaemia may occur in association with cirrhosis de Castro s patient had sprue

At one time all macrocytic anaemias were classed together and said to be due in some way to a lack of the anti pernicious anaemia principle the macrocytic anaemia of liver disease was ascribed to an inability of the damaged liver to store or manufacture this substance The normoblastic erythropoiesis now known to be present in the great majority of cases rules out this hypothesis As we have seen in cases of cirrhosis true megaloblastic erythropoiesis can occur but it is not due to the liver disease itself moreover the administration of vitamin B_{12} or folic acid produces either no effect or a slight reticulocyte rise such as may follow the administration of substances of no haematopoietic potency Antipernicious anaemia principle has been extracted from the livers of cirrhotic patients by Schiff Rich and Simon (1938) There is thus no evidence that deficiency of the anti pernicious anaemia prin ciple is in any way responsible for the macrocytic anaemia of cirrhosis

In certain cases of cirrhosis there has been striking evidence of excessive haemolysis In a recent study Chaplin and Mollison (1953) have shown a reduced red-cell life span in all of five patients with advanced hepatic cirrhosis These authors also showed that although

red cell production was greater than normal there was nevertheless defective marrow output as compared with that to be expected from a normal marrow As a result of liver failure circulating metabolites in abnormal amounts or of abnormal constitution may influence the maturation of marrow tissue The red-cell precursors are well haemo globinated the major changes appear to be in the nuclei The influence of cirrhotic serum upon the maturation of normal bone marrow cells in tissue culture would be a most interesting study

Unfortunately no specific therapy exists for the treatment of the anaemia of cirrhosis treatment of the liver disease itself along the lines recommended in Chapter 5 is all that is likely to be of value It is tempting at the present time to ascribe anaemia in cirrhosis with portal hypertension to hypersplenism That the congested enlarged spleen of portal hypertension may have some occult influence on the bone marrow, or may exert an enhanced phagocytic effect is undoubted Hyman and Southworth (1951) state however that splenectomy is of no therapeutic value in patients with haemolytic anaemia associated with hepatic cirrhosis Not only is splenectomy in the presence of severe parenchymatous liver disease a hazardous procedure but far too little is known of the precise role of the spleen if any in the anaemia of cirrhosis to make splenectomy a justifiable procedure in the great majority of cases

The Anaemia of Renal Disease

Anaemia is a well recognized clinical feature of chronic renal disease of whatever aetiology This discussion does not cover those transient but often very dramatic variations in haematocrit value resulting from plasma changes during diuresis in patients with oedema These volume changes may be further complicated by heart failure (Harris and Gibson 1939) In some instances blood loss is a major factor and in others the anaemia of infection may be superimposed It must be remembered also that the severity of the anaemia may not be apparent from the red cell count and haemoglobin since in subacute or chronic nephritis with or without congestive heart failure the plasma volume may be above and the circulating red cell and total blood volume below normal values (Harris and Gibson 1939) Since anaemia is most commonly found and is most pronounced in those patients in whom renal failure has developed it is usually ascribed to a depression of haemopoietic tissue by retained metabolic products though what specific substance or substances are responsible is unknown There seems to be a rough correlation between the degree of nitrogen retention and anaemia

The anaemia is usually slowly progressive and is not accompanied by evidence of increased red cell destruction nor is there evidence of

an intrinsic erythrocyte defect (Loge Lange and Moore 1950) On the other hand it has all the characteristics of an anaemia due to decreased haematopoiesis Recently evidence favouring this concept has come from studies which demonstrate a depression of normal marrow-cell growth by culture *in vitro* with serum from patients suffering from the anaemia of renal failure (Sacchetti 1953) While this is the common finding other patients are seen in whom anaemia may become very rapidly progressive In these patients an extracorpuscular haemolytic factor is evident from the shortened survival of transfused normal cells and the normal survival of patients cells in normal recipients (Loge *et al* 1950) The activity of this factor is most pronounced in cases of severe renal failure its nature is unknown A diminished erythrocyte life span has recently been confirmed in 5 out of 6 patients with advanced renal failure by Chaplin and Mollison (1953) a defective red-cell production was also demonstrated both in these patients and in three others with less advanced renal disease in whom the red-cell life span was not reduced Recently the anaemia of renal disease has been treated with cobaltous chloride (Gardner 1953) While the anaemia may respond after some one to two months delay it is doubtful if the degree of clinical improvement attained in most patients is of much value

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SOME DISORDERS ASSOCIATED WITH ABNORMALITIES OF PROTEIN METABOLISM

Multiple Myelomatosis

Following the development of new techniques such as paper electrophoresis for the study of serum proteins there has been a renewal of interest in the remarkable abnormalities of protein metabolism so often seen in myelomatosis It will be convenient to discuss the proteins found in the serum first and then to comment upon those excreted in the urine

In some cases of myelomatosis it is the amount of protein in the serum which is at first sight the most remarkable feature, concentrations of over 10 g per cent are quite frequent and values of over 20 g per cent have been recorded High serum protein levels are often stated to be the cause of the high serum-calcium values sometimes encountered in myelomatosis This is, however an unlikely explanation for the protein increase involves the globulin fraction which only binds calcium with about one fifth the effectiveness of albumin It seems more probable that calcium is liberated into the blood stream from extensive osteolytic lesions when the serum calcium is high there is hypercalcuria and renal calculi may result (Snapper 1943 Albright and Reifenstein 1948) In some cases impairment of renal function may be an additional factor in raising the serum calcium level

Serum inorganic phosphorus levels are usually either normal or especially if there is renal failure raised low values are very rarely encountered The alkaline phosphatase is usually normal this would be expected for the bone lesions of myeloma are osteoclastic, slightly raised values are however said to occur especially in patients with extensive fractures Acid phosphatase levels are normal These features are sometimes of assistance in the diagnosis of certain cases of myelomatosis which show clinical and radiological features very suggestive of hyperparathyroidism

Hyperproteinaemia is responsible for the rouleaux formation and high sedimentation rate which are commonly found in cases of myelomatosis It is however not the amount of protein but its character which is of the greatest interest In 220 cases collected from the literature 75% showed diagnostic serum electrophoretic patterns (Osserman and Lawlor 1955) The commonest pattern is an increase in gamma globulin much less commonly there is an increase in beta globulin Cases where both beta and gamma globulins are increased are exceptional Sometimes the exact type of globulin is difficult to determine and several workers have noted cases with a mobility between that of gamma and beta globulin (Rundles, Dillon and Dillon

1950) Chadbourn and Zinneman (1955) designate this the M pattern three of their 27 patients produced protein of this type The shape of the peaks in myelomatosis is often very suggestive they are usually very sharp and narrow quite unlike the much more diffuse gamma globulin peaks seen in certain chronic infective processes (see below)

During the course of the disease in any one patient only a single protein of electrophoretically homologous type is to be observed Both beta and gamma fractions may consist of proteins with different sedimentation constants on ultracentrifugation however there is no specific myeloma globulin characteristic for all cases of myeloma

Differences in amino acid composition have been reported between proteins of the same electrophoretic mobility (Grisolia and Cohen 1953) they have also been shown to differ by immunochemical methods (Wunderly Gloor and Hassig 1953)

About 20 per cent of patients show no significant electrophoretic abnormality in the serum (Gutman Moore Gutman McLellan and Kabat 1941 Kekwick 1940 Wuhrmann Wunderly and Hugentobler 1949 Osserman and Lawlor 1955) As Gutman *et al* (1941) pointed out these cases of normoproteinaemic myeloma often excrete con siderable quantities of Bence Jones protein in the urine Very occasional cases are met with where there is neither serum abnormality nor proteinuria so that normal serum proteins cannot always be accounted for by loss in the urine Cases of myelomatosis with increases in alpha globulin were reported by Wuhrmann Wunderly and Wiedemann (1948) but are not too well documented There is some doubt of their true nature and they have been but rarely encountered by others Rundles *et al* (1950) correlated a rise of alpha globulin in some of their cases with a general tissue reaction and possibly with hepatic cellular damage Osserman and Lawlor (1955) also comment on moderate increases in the alpha globulins of a non specific nature

Non specific albuminuria occurs sometimes in myelomatosis and may appear in sufficient quantity to obscure the characteristic Bence Jones protein It would perhaps be better to use the term Bence Jones proteins for their physico-chemical properties are very diverse (Putnam and Stelos 1953) A molecular weight of about 36 000 is often quoted (Svedberg and Sjogren 1929) this figure is criticized by Putnam and Stelos (1953) who found different samples of the protein to vary greatly but four of their specimens appeared to have molecular weights of about 43 000 It has been crystallized and variations in crystal form in samples from different patients also indicate that all specimens are not identical

Bence Jones proteins must be transported by the blood stream and so must occur in the serum in all cases where they are present in the urine They are very difficult to detect in the serum however and if

detectable at all they are found only in very small quantities This is readily accounted for by their small molecular weight they have been shown to pass easily through cat or rabbit kidney while normal serum proteins were retained (Kerridge and Bayliss 1932)

If Bence Jones protein is added to serum an additional electrophoretic peak appears in a different position to the gamma globulin (Rundles *et al* 1950) Isotopic studies carried out by Hardy and Putnam (1953) would indicate independent turnover rates for the two types of protein The fact that Bence Jones proteins of different immunological type and different electrical mobility can be demonstrated in serum is further evidence that these proteins are synthesized as such and that they are not, as has been suggested, simply plasma proteins modified in some way by the kidney Osserman and Lawlor (1955) suggested that myeloma serum globulins may be conjugated glycoproteins since after separation by filter paper electrophoresis they give an intense periodic Schiff reaction Urine myeloma proteins however are Schiff negative Although this could be explained by postulating that removal of the carbohydrate moiety from the serum glycoprotein allowed excretion in the urine of the protein constituent it could also be taken to support the idea of an independent origin for urinary and serum myeloma proteins The frequent though not invariable occurrence of massive Bence Jones proteinuria in association with no demonstrable electrophoretic abnormality in the serum would also be most readily explained by an independent synthesis of Bence Jones proteins Very important evidence also pointing to this conclusion was produced by Dent and Rose (1949) They investigated a patient who was excreting on an average 36 g of Bence Jones protein a day This protein contained no detectable methionine and so differed strikingly from normal plasma protein This has been confirmed by Agren (1949) Papastamatis, Kench and Wilkinson (1949) and Roberts Ramasarma and Lewis (1950) All the evidence would indicate therefore that Bence Jones proteins are produced quite independently of normal plasma proteins and of the abnormal globulins found in the serum in multiple myelomatosis

The proliferating plasma cells which are the most striking histological feature of myelomatosis are almost certainly the source of the remarkable proteins discussed above The amount of protein is often related to the anatomical extent of the disease (Rundles *et al* 1950) In those cases in which regression of plasma cell tissue follows therapy the abnormal proteins coincidentally decline in amount The intense basophilia so characteristic of the cytoplasm of plasma cells is related to an abundance of ribose nucleic acid, an appearance associated with protein synthesis Abnormal globulins have been isolated from myeloma tissue by several workers and in each case it has been found that extracted globulin and serum globulin from the same patient had the

same electrophoretic pattern (Martin 1947 Lane 1952 and Miller Brown Miller and Eitelman 1952)

Many attempts have been made to correlate the clinical picture course of the disease and type of plasma cell with the electrophoretic pattern and the presence or absence of Bence Jones proteinuria Very varied views have been expressed on this subject Rundles *et al* (1950) found no relation between the morphology of the plasma cells and the type of protein abnormality or the susceptibility to treatment by urethane Osserman and Lawlor (1955) were also unable to correlate clinical or pathological features on the one hand with the type of electrophoretic pattern on the other Kubota Schwartz and Putnam (1956) in a study of 78 cases came to the same conclusion In a study of living myeloma cells by ultraviolet microscopy Olhagen Thorell and Wising (1949) were able to differentiate two types of cell One showed a small nuclear-cytoplasmic ratio and an appearance similar to the nature plasma cell it was associated with an increase of beta or gamma globulin in the serum The other type showed a large nuclear cytoplasmic ratio and heavily absorbing nuclei and nucleoli here the electrophoretic pattern was normal and Bence Jones proteinuria was present Three cases had both types of cell and both had increased serum globulin and Bence Jones protein More recently Chadbourne and Zinneman (1955) have correlated small size and small amount of cytoplasm with an increase in beta globulin Plasma cells of large size and with a large amount of cytoplasm were found in cases showing a gamma or intermediate globulin pattern These findings are similar to those of Waldenstrom (1952)

The concentration of abnormal serum proteins has not usually been significantly reduced by roentgen therapy P^{32} or stilbamidine (Adams Alling and Lawrence 1949) Thorn Forsham Frawley Hill Roch Stachelin and Wilson (1950) report a case of myeloma in which, under the influence of ACTH the serum globulin decreased and plasma cells coincidentally disappeared from the marrow In other cases either no effect was observed at all or there were changes in serum proteins without any decrease of plasma cell proliferation (Effersoe 1950) Rundles *et al* (1950) have reported cases of myeloma treated with urethane in which after a latent period of about one month there was a very striking disappearance of abnormal serum proteins and a coincident rise of albumin to normal As Waldenstrom (1952) suggests in this and other disorders accompanied by a high serum globulin the low albumin may be due to a diverted protein synthesis and not due to an inability of damaged tissue to synthesize albumen

For a discussion of the renal lesions of myeloma the reader should consult Blackman Barker Buell and Davis (1944) and Armstrong (1950)

The Nature of Multiple Myelomatosis An increase in gamma globulin is found in certain chronic infective processes for instance lympho granuloma kala azar experimental immunization cirrhosis and in certain collagen diseases The gamma globulin peak in these cases is broad and quite unlike the sharp peak which is so characteristic of myeloma These disorders are also associated with marked plasma-cell proliferation This when taken with the known association of gamma globulin fraction with antibodies has led to the suggestion that myeloma may be primarily due to an unbridled response to a chronic infective process This aspect is fully discussed by Waldenstrom (1952) Very interesting evidence which would support this view is presented in the paper by Dent and Rose (1949) quoted above Absence of methionine is a feature of virus proteins and they suggest tentatively that in myelomatosis there may be an intense proliferation of virus in the plasma cells which stimulates their growth they also suggest that Bence Jones protein may be the virus itself minus nucleic acid The amount of protein which may be produced is not, in their view against this hypothesis The similarity to virus protein is made even closer by the observation that both have relatively high aliphatic hydroxy amino acid contents (Roberts *et al* 1950) The view that myelomatosis is a neoplastic disease is still generally accepted however certainly the age incidence and course of the disease would favour this outlook The viral hypothesis is however a very interesting and stimulating one and may well lead to important advances

Cryoglobulinaemia

This is a remarkable abnormality of protein metabolism charac terized by the presence in serum of a protein reversibly precipitable by cold This precipitation is most likely to take place at temperatures of between 4 and 11 C but may occasionally occur at 32–33 C (Rorvik 1950) The process is sometimes referred to as clotting, but it is in no way related to true coagulation and is as has been stated reversible A cold environment may result in protein precipitation in peripheral vessels and give rise to vascular stasis with purpura oedema and in severe cases necrosis and gangrene of the extremities This occurrence is often loosely referred to as the Raynaud syndrome to the essential features of which however it bears no resemblance This aspect has been especially studied by Hansen and Faber (1947) who describe a characteristic skin reaction to cold The blood sedimentation rate is very rapid at 37 C and marked rouleau formation usually occurs at low temperatures when the globulin has precipitated sedimentation is of course nil—a reverse of the findings in the cases of cold agglutina tion

The condition is most commonly found in cases of multiple myelo

matosis (Wintrobe and Buell 1933 Barr Reader and Wheeler 1950) It has also been observed in chronic lymphatic leukaemia (Schwartz and Jager 1949 Craig Waterhouse and Young 1952) and may occur in a large group of chronic infections (Lerner and Watson 1947 Lerner Barnum and Watson 1947) Among conditions with which it has been associated are the following kala azar malaria subacute bacterial endocarditis (Dreyfuss and Librach 1952) erythema multiforme serum sickness rheumatoid arthritis periarteritis nodosa and hepatic disease The sera of patients with macroglobulinaemia may also contain cryoglobulins

Macroglobulinaemia

This remarkable disorder was described by Waldenström (1944) The plasma of these patients contains a very unusual globulin of a very high molecular weight this has on ultracentrifugation a sedimentation constant of about 19 to 20 S The molecular weight is about 1 million Macroglobulins most commonly move with the electrophoretic mobility of gamma globulin but as in myelomatosis variations are reported A very simple screening test is performed by letting a drop of serum fall into distilled water when if macroglobulins are present an intense white flocculent precipitate will form this dissolves on adding saline but will reprecipitate on adding distilled water The commonly used euglobulin tests are usually positive also (Takata ara cadmium thymol turbidity and Weltmann)

Elderly men are most commonly affected although the disorder has been recorded in a man of 21 years (Wilde and Hitzelberger 1954) The course is usually very chronic There is most often a story of gradually developing weakness and loss of weight with occasional bouts of fever These patients frequently present with purpura this may be due to thrombocytopenia but quite diverse abnormalities of the clotting mechanism may be found In some cases the purpura seems to be due to an increased capillary fragility alone The central nervous system may also be involved The changes are not at all specific they are usually due to haemorrhage or to vascular lesions resulting from perivascular infiltration with plasma cells lymphocytes reticuloendothelial cells or mast cells (Bichel Bing and Harboe 1950) Retinal haemorrhages have several times been reported Epistaxis and bleeding gums are mentioned in several case reports A moderately severe normochromic anaemia is common white-cell changes are not specific A high and sometimes extremely high sedimentation rate seems to be invariable Other clinical features include vascular disturbances of the extremities enlarged non tender lymph nodes hepatosplenomegaly and oedema

Macroglobulinaemia may be primary but it may also occur as a secondary phenomenon in such conditions as nephrosis and lupus

erythematosis (Waldenstrom 1952). It is interesting to find that it may occur with cryoglobulinaemia (*vide supra*) and that both of these paraproteins may occur in myelomatosis as well as the more usual protein abnormalities of that disease. Unlike Bence Jones protein the methionine content of one sample of macroglobulin was found to be the same as that of human gamma globulin (Mandema van der Schaaf and Huisman 1955). In primary macroglobulinaemia there may be a plasmocytosis of the bone marrow the type of plasma cell found makes confusion with myelomatosis unlikely. The very long clinical course of the disease is also quite unlike that of myeloma and beyond slight generalized decalcification in no reported cases have there been any radiological changes in the bones bone pain has never been described. In other cases the appearance of the marrow may be indistinguishable from that of chronic lymphatic leukaemia other reports mention hypoplastic or normal marrow histology. Tischendorf and Hartmann (1950) have recorded a case with mast-cell hyperplasia.

There is some evidence that the macroglobulinaemia and the sedimentation rate may sometimes return to normal on cortisone therapy (Wilde and Hitzelberger, 1954) in other patients cortisone has had no effect. The condition has been well reviewed recently by Jim and Steinkamp (1956).

Purpura Hyperglobulinaemica

This additional example of dysproteinaemia was also first described by Waldenstrom (1948). It is characterized by the presence in the plasma of large amounts of a gamma globulin which on ultracentrifugation is found to belong to the S 7 protein component. The protein peak on electrophoresis is rounded and resembles more the gamma globulin peaks seen in chronic infections (*vide supra*) than those of myeloma there is a normal albumin content. The disorder unlike macroglobulinaemia is more common in women. The disease is very chronic there is a high sedimentation rate purpura with resultant pigmentation is most marked on the legs a moderate lymphadenopathy and hepatosplenomegaly may be found. The marrow is usually normal there is a moderate normochromic anaemia. There is an increased capillary fragility but as in other dysproteinaemias very complex clotting effects also occur. References are given by Waldenstrom (1952). A recent discussion has been published by Taylor and Battle (1954).

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THE MEGALOBLASTIC ANAEMIAS

This group of disorders is characterized by the common morphological feature of megaloblastic erythropoiesis although the most

striking changes are seen in the red-cell series white cells and platelets are also affected though usually to a lesser extent Changes of a similar type have also been reported in the gastric mucosa which like those in the bone marrow can be completely reversed by vitamin B_{12} therapy (Graham and Rheault 1954) This megaloblastic change is the visible manifestation of a widespread biochemical disorder, it may result from a pure vitamin B_{12} deficiency as in Addisonian megaloblastic anaemia or from a pure folic-acid deficiency as in megaloblastic anaemia of pregnancy as seen in temperate climates In other disorders such as sprue the deficiency is often mixed The treatment of disorders associated with a pure deficiency is easy and the results are usually excellent that of combined deficiencies is less satisfactory it may well be that in such cases other as yet unrecognized substances are also lacking An account will be given first of the nature and functions of vitamin B_1 and folic acid which will be followed by a very brief account of the disorders with which deficiency of these substances is associated A very full discussion of the megaloblastic anaemias has recently been published by Davis and Brown (1953)

Vitamin B_{12}

The therapeutic effect of liver in Addisonian pernicious anaemia was first described by Minot and Murphy in 1926 During the next twenty years many attempts were made to obtain pure antipernicious anaemia principle although potent extracts were prepared in bulk for clinical use it was not until 1948 that the principle itself was isolated in the pure crystalline form and named vitamin B_{12} (Rickes Brink Koniusky Wood and Folkers 1948 Lester Smith 1948) It is now known to have a molecular weight of 1357 5 a value more than twice as great as that of any other known vitamin It is interesting to find that vitamin B_{12} has a nucleotide structure which recalls that of several known co enzymes Diphosphopyridine nucleotide or co-enzyme I for instance consists of nicotinic acid linked to ribose phosphate and adenine In place of adenine the vitamin B_{12} molecule contains the related substance 5 6-dimethylbenziminazole linked to ribose This is linked by phosphate to the rest of the molecule This part has a superficial resemblance to haem for there is a porphyrin like ring structure with an atom of cobalt at the centre in place of the iron atom of haem The four rings of vitamin B_{12} are not true pyrrole rings however and although three of them are linked by meso -carbon bridges the fourth linkage is direct in the α position As in haem the porphyrin like rings have side chains three of these are acetamide three propionamide and one probably dimethyl The bridge structure mentioned above links one propionic acid side chain to isopropanolamine which is esterified by phosphoric acid which links it in turn to the ribose (Hodgkin Pickworth Robertson

Trueblood Prosen and White 1955 Bonnett Cannon Johnson Sutherland Todd and Smith 1955) Many other factors are known which are closely related to vitamin B_1 these are discussed by Kon (1955)

Vitamin B_1 is active therapeutically in Addisonian megaloblastic anaemia in microgram doses when administered parenterally or when given orally with a potent source of gastric intrinsic factor Although haematopoietic responses have been observed after oral administration of the vitamin alone the amounts necessary are measured in milligrams and are quite impracticable for clinical use (Ungley 1951–2) While patients have been maintained on daily oral doses as small as 50 μg (Chalmers and Hall 1954) it is generally agreed that such therapy may be inadequate to protect against subacute combined degeneration of the cord and is not to be recommended for general use According to the original theory of Castle a substance in the diet (extrinsic factor) interacts with a substance in normal gastric juice (intrinsic factor) to form the anti pernicious anaemia principle which is then stored in the liver and is available for use by the tissues Castle s theory has had to be modified however for it is now apparent that vitamin B_1 itself fulfils the criteria for extrinsic factor in that it is a substance which when given orally to patients suffering from Addisonian pernicious anaemia in relapse is haematopoietically active in minute amounts only if accompanied by intrinsic factor from normal gastric juice at the same time the vitamin has all the attributes of Castle s anti pernicious anaemia principle It thus appears that extrinsic factor and anti pernicious anaemia principle are one and the same substance It is also clear that intrinsic factor must as was originally suggested by Castle play a vital role in the absorption of vitamin B_{12} from the intestinal tract Many attempts have been made to isolate intrinsic factor and fairly concentrated preparations have been obtained It is a mucoprotein with a molecular weight of about 15 000 the present state of knowledge regarding its properties has been reviewed by Latner (1955) and by Thompson and Ungley (1956) Preparations of intrinsic factor can be tested by their ability to potentiate the haematopoietic effect of orally administered vitamin B_1 or by their effect on the absorption and ex cretion of orally administered radioactive vitamin B_{12} (Welch Scharf Heinle and Meacham 1952) Intrinsic factor is present in the fundus and cardia of the healthy human stomach (Fox and Castle 1942 Landboe Christiansen and Plum 1948) It is not present or exists only in traces in the stomachs of patients with Addisonian pernicious anaemia such patients have a permanent atrophy of the intrinsic factor bearing area of the stomach (Magnus and Ungley 1938) This atrophy may sometimes be genetically determined there is evidence that it is more frequent in some races than in others and Wilkinson

(1949) found that 308 of his 1600 cases gave a history of at least one patient in the family

Recent evidence suggests that atrophy of sufficient severity to cause deficient intrinsic factor production may follow chronic inflammatory disease of the gastric mucosa (Palmer 1954 Joske Finkh and Wood 1955 Markson and Davidson 1956) This gastric atrophy may be detected during life by the biopsy method of Wood Doig Motteram and Hughes (1949) For practical clinical purposes the finding of free acid after a histamine and alcohol test is taken to imply the presence of intrinsic factor also and to exclude a diagnosis of Addisonian megaloblastic anaemia the converse of this is not always true however An unusual case of defective intrinsic factor production with a histologically normal gastric mucosa and secretion of normal amounts of pepsin and acid has been reported by Mollin Baker and Doniach (1955) Until recently it was thought that the function of intrinsic factor was to bind vitamin B_{12} in some way this binding allowed the vitamin to be more readily absorbed and at the same time rendered it unavailable to intestinal bacteria (Burkholder 1952) Although bacteria utilizing vitamin B_{12} for their growth are absent from the intestinal tracts of normal persons it has often been claimed that they are present in those patients with atrophic conditions of the gastric mucosa It seems that the evidence for this will have to be reassessed as a result of recent investigations (Cregan Dunlop and Hayward 1953) Preparations of purified intrinsic factor however while greatly enhancing the absorption of vitamin B_{1} have been shown to possess little if any binding capacity At present the function of intrinsic factor is considered to be solely one of enhancing the absorption of vitamin B_{12}

The vitamin is probably absorbed mainly in the duodenum Whether given parenterally or orally with or without intrinsic factor vitamin B_{12} is found in the serum bound to the globulin fraction The bound vitamin which is present in serum after parenteral administration is presumably formed by interaction with some serum binding factor much as iron is carried in the blood stream by the specific iron binding protein but that this binding of vitamin B_{12} is specific is unproved When very large doses of the vitamin are given much of it appears in the urine as is the case with iron it may be that the serum binding factor can deal with only limited intakes though other explanations are possible It is at present considered probable that only in the bound form is the vitamin available to the tissues this is certainly suggested by the marrow culture experiments of Callender and Lajtha (1951) Values for total vitamin B_{12} concentration in serum for a group of normal subjects ranged from 100 to 720 $\mu\mu$g /ml (mean 358) the bound concentration was from 100 to 620 $\mu\mu$g /ml (mean 329) (Mollin and Ross 1952) Similar values were found in a series of patients suffering

from conditions other than megaloblastic anaemia In megaloblastic anaemias responsive to vitamin B_{12} the serum values are well below the normal range In anaemias refractory to vitamin B_{12} but folic acid responsive such as megaloblastic anaemia of pregnancy normal values are found (Mollin and Ross 1952 Rosenthal and Sarett 1952)

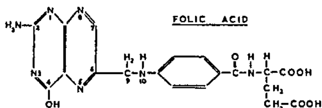
Vitamin B_1 is stored in the liver, which was until recently the sole commercial source Although some organisms utilize the vitamin for their growth others produce it in large quantities and it is now prepared by extraction from the medium in which streptomyces griseus grows Indeed organisms in the colon of patients with Addisonian pernicious anaemia may produce sufficient of the vitamin to produce a remission of their disease were they able to absorb it efficiently from this site (Callender and Spray, 1951)

Folic Acid and Folinic Acid

Folic acid was first discovered in 1941 and was synthesized four years later it is known to be pteroylglutamic acid (PGA) and consists of a pteridine linked to glutamic acid by *p* aminobenzoic acid (Fig 4) It is essential for normal haematopoiesis the most striking clinical manifestation of its deficiency is a megaloblastic anaemia the disorders in which such deficiency occurs are discussed below Normal body requirements are obtained from fresh green vegetables liver kidney certain cereals and meat (Toepfer Zook and Orr 1951) The exact relationship of synthetic folic acid to that obtained from these natural sources is as yet not clear but most of the naturally occurring substance is in the form of conjugates specific folic acid conjugates exist in most animal tissues which release free folic acid from these more complex forms and make it directly available

Unlike vitamin B_1 folic acid is haematopoietically active in all megaloblastic anaemias the true nature of certain exceptionally rare instances of folic-acid refractory megaloblastic anaemia which have been reported is very uncertain It cannot be too firmly emphasized however that folic acid must be used only in patients suffering from a folic acid deficiency it should never be used for instance in Addisonian pernicious anaemia where there is a pure deficiency of vitamin B_{12} although an initial haematopoietic response will occur in such patients it is unlikely to be maintained More important is the observation that folic acid is not effective in relieving the neurological complications of Addisonian pernicious anaemia and will not prevent their occurrence Moreover subacute combined degeneration of the spinal cord may develop very rapidly during folic acid administration it is thought likely that a very acute vitamin B_{12} deficiency develops under these circumstances

In 1948 a factor was discovered which is essential for the growth of



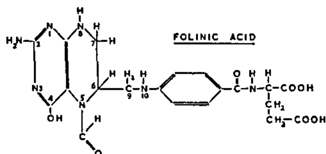
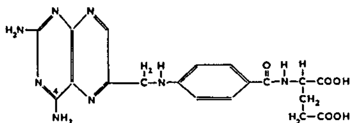
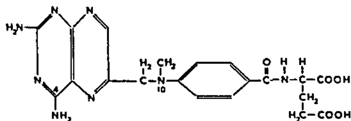


FIG 4



AMINOPTERIN



A METHOPTERIN

FIG 5

the organism leukonostoc citrovorum (Sauberlich and Baumann) This substance, known as the citrovorum factor (CF) is tetrahydroformyl folic acid (Fig 4) and is believed to be the active form of folic acid

The interrelationships of folic-acid derivatives and their precise roles in metabolism are by no means clear the subject has been reviewed recently by Greenberg (1954) Folinic acid can be formed from folic acid in the body for this conversion ascorbic acid appears to be essential (Nichol and Welch 1950a Gabuzda, Phillips Shilling and Davidson 1951) Folinic acid is therapeutically effective in the megalo blastic anaemias, the indications for its use are the same as for folic acid

Several antagonists to folic acid (strictly speaking to folinic acid) have been developed two of the best known are aminopterin and *a* methopterin As can be seen from Fig 5, the essential structure of folic acid is retained in both of the antagonists however an amino group is attached to position 4 and in *a* methopterin a methyl group is also attached to position 10 Such substances interfere with the activa tion of folic acid to folinic acid in the body (Nichol and Welch 1950b) The deficiency of the active form of folic acid produced by their ad ministration occasionally results in the appearance of megaloblast like cells in the bone marrow overdosage results in aplasia These antago nists have therapeutic value in the treatment of neoplastic diseases particularly the acute leukaemias where they probably interfere with nucleic acid synthesis in the rapidly dividing cells (*vide supra*)

The Functions of Vitamin B_{12} and Folic Acid

In the megaloblastic anaemias the most striking morphological abnormality is in the nuclei of the red cell precursors in the bone marrow Nuclear abnormalities are also seen in the white cell series which are less pronounced but very characteristic In a number of different haematological disorders White Leslie and Davidson (1953) found significant differences from the normal values for desoxyribo nucleic and ribonucleic acid phosphorus only in the megaloblastic anaemias they discuss the possibility that there may be a disturbance of mitosis to account for this observation There is also much evidence to point to a fundamental defect of nucleic acid synthesis in the megalo blastic anaemias The nucleic acids are substances of immense bio logical importance they are present in all biological entities capable of reproduction, a process with which they are closely associated On complete hydrolysis they yield purine and pyrimidine bases a pentose sugar and phosphoric acid The sugar is either ribose or desoxyribose those nucleic acids containing desoxyribose (DNA) are found only in the nucleus where they are one of the major constituents of the chromo somes Ribose nucleic acids (RNA) are found mainly in the cytoplasm

but also occur in small amounts in the nucleus especially in the nucleolus The purine bases are adenine and guanine (Fig 6) and occur in both DNA and RNA The pyrimidine bases are cytosine also found in both types uracil found only in RNA and thymine found only in DNA The sugar moiety is attached to purines at position a and to

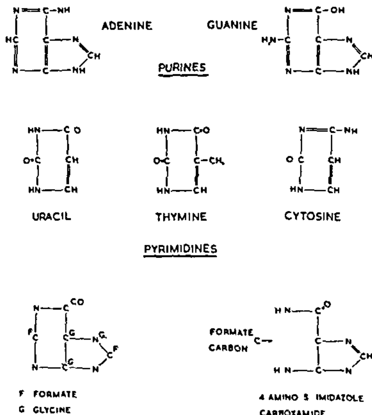


Fig 6

pyrimidines at position 3 such a compound is known as a nucleoside The nucleic acids themselves are highly polymerized chains of the phosphoric esters of nucleosides—the nucleotides Apart from the nuclei of cells many other very important compounds have the structure of nucleotides Examples are vitamin B_{12} the nicotinamide nucleotides and co-enzyme A It is interesting to note that Welch and Heinle (1951) have suggested that folinic acid may also be conjugated with ribose phosphate

Studies with radioactive tracers have shown that the purine and

pyrimidine bases are synthesized from simple substances such as ammonia formate carbon dioxide glycine and serine (Fig 6) It is doubtful if dietary purines can be utilized as such and the same probably applies to pyrimidines Both vitamin B_1 and folic acid are necessary for *purine and pyrimidine synthesis Their functions are probably closely* related both microbiological and clinical evidence suggests that both substances are required for nucleic acid synthesis They evidently act at different stages and are not interchangeable Both folic acid and vitamin B_1 are probably involved in the transfer and synthesis of single *carbon units The function of vitamin B_{12} has been reviewed recently by* Arnstein (1955) that of folic acid by Greenberg (1954) It is probable that the formate group of folinic acid is involved in transfer processes One piece of evidence may be cited When sulphonamides inhibit the synthesis of purines by Escherichia coli 4 amino 5 imidazole carboxamide is found to accumulate in the medium As can be seen in Fig 6 the addition of a single carbon unit as from formate to this substance could result in the closure of the ring and the formation of a purine Greenberg (1950) has shown that folic acid and formate are in fact essential for this reaction

Disorders with which Megaloblastic Erythropoiesis is Associated

Addisonian Megaloblastic ('Pernicious') Anaemia

The aetiology of this condition has already been discussed It is felt that the name pernicious should now be dropped the eponym is well worth retaining as it serves both to honour the name of Addison and to distinguish the classical variety of megaloblastic anaemia from the many other types now recognized The clinical picture and haematological features of the disorder are too well known to be described here an excellent recent account is given by Davis and Brown (1953) Treatment should now be by vitamin B_{12} which is readily available cheap and being a pure substance can be given in an accurate and known dosage There is now no place for liver extracts and the use of such oral medicaments as hog s stomach are quite unjustified Commercial preparations of vitamin B_1 and intrinsic factor are available and have *been shown capable of maintaining patients with Addisonian* megaloblastic anaemia in remission (Lowther Alexander and Hendry 1954) At the present time however, there is no satisfactory substitute for parenteral administration of vitamin B_{12} for the average patient as dealt with in clinical practice No reports have appeared of sensitivity to vitamin B_{12} The initial dosage advised in the average uncomplicated case is 100 μg per week until normal blood values are attained when the interval can be lengthened to a month Some patients can be maintained on *100-μg doses at even greater intervals but these are not to be*

recommended for general use This dosage is no doubt in excess of requirements but parsimony has nothing to commend it If subacute combined degeneration is present 100 μg should be given weekly or twice weekly for at least six months for in that time most of the ex pected improvement will occur (Ungley 1949) In severe cases with incontinence urinary infections pneumonia or other complications which in some patients undoubtedly retard the response to vitamin B_{12} more frequent initial doses may be used There is little point in giving very large doses for most of the vitamin will be lost in the urine Patients on maintenance treatment should ideally be examined and a blood count carried out at six or twelve monthly intervals Espe cially in women supplementary treatment with iron may be neces sary the rapid increase in the red-cell count may deplete deficient iron stores

That other types of megaloblastic anaemia differing from the classical Addisonian variety exist has been recognized for a long time it is only since pure haemopoietic preparations became available that it has been possible to differentiate these at all clearly a brief account follows

The Sprue Syndrome

While anaemia is common in this disorder it is often hypochromic and associated with a normoblastic marrow picture A megaloblastic anaemia is well recognized however in both the tropical variety and in so-called non tropical sprue as encountered in temperate climates it is commoner in the former disorder While the bone marrow usually shows typical megaloblastic erythropoiesis cases have often been described in which so-called intermediate megaloblasts are found (Dacie and White 1949) these cases respond to treatment as do those showing typical megaloblastic change the bone marrow cells becoming normoblastic The permanent gastric atrophy so characteristic of Addisonian megaloblastic anaemia is not found Achlorhydria is in constant and even if found initially may not be permanent While in some patients the evidence of intestinal disease is very obvious in others fat balance studies may be required for its demonstration In any patient with non Addisonian megaloblastic anaemia in whom the exact diagnosis is uncertain such studies are essential (Cook Peeney and Hawkins 1953) It is probable that most of the patients reported as suffering from so-called achrestic anaemia had occult steatorrhoea It is easy to account for the development of anaemia by malabsorption of haematopoietic factors The aetiology may not be as simple as this however and the relationship of infective processes in the affected intestine to the development of anaemia has aroused much interest the extent of this influence has as yet to be assessed The deficiency

may be of folic acid or of vitamin B_1 alone, but is more frequently mixed deficiency of folic acid being usually more prominent Patients should be treated initially with vitamin B_{12} if the haematopoietic response is complete the patient should be maintained as long as necessary on this treatment alone More often an initial response occurs which is submaximal when compared with that expected in a case of Addisonian megaloblastic anaemia of equal severity and normal blood counts are not attained If folic acid is then given a second response will usually occur and normal values may be reached In cases showing a dual deficiency both vitamin B_{12} and folic acid should be given for maintenance treatment Cases of non tropical sprue usually require indefinite maintenance they are always liable to relapse Patients who have suffered from tropical sprue and who have returned to a temperate climate are more likely to remit permanently Unfortunately in non tropical sprue whatever treatment is given it is sometimes impossible to obtain full remission of the anaemia possibly other as yet unknown haematopoietic agents are also missing but the anaemia may also be due to general metabolic disturbances Deficient iron absorption is very likely to be present and is a further cause of poor remission of anaemia or of relapse General dietary measures are also essential as well as full vitamin supplements There is very frequent deficiency of calcium which must be corrected low prothrombin levels are also often encountered

Anatomical Lesions of the Small Intestine

This is a rare cause of megaloblastic anaemia but one of very great theoretical interest it has been the subject of recent studies by Cameron Watson and Witts (1949a and b) and Thompson and Ungley (1954) In the writer s experience it is always associated with a deficiency of vitamin B_{12} The anatomical lesion may be the result of disease as in strictures of the lower ileum or regional ileitis or may result fro[m] surgical procedures in which blind loops of small intestine are pro[-] duced The production of such blind loops of small intestine are pro[-] in the direction of the blind end is the most effective method of pro[-] ducing a comparable anaem[ia] ... factor in ... [illegible]

stasis [illegible] cases see[m] [illegible] imental animals The common reaches [illegible] in [illegible] dly to be the occurrence of their gro[wth] [illegible] intest[ine] [illegible] tine Infection of the upper the [illegible] [illegible]unt [illegible] utilizing vitamin B_{12} for [illegible] of the [illegible] of a deficiency state [illegible] to increased demands for [illegible] is [illegible] this type of anaemia to [illegible] in both disorders [illegible] intestine However [illegible] of such infec

tions has yet to be assessed The anaemia may respond to correction of the anatomical defect but this is not always practicable unfortunately many patients live a semi invalid existence very similar to that of some sufferers from the sprue syndrome Maintenance treatment is required in those cases where restitution of the anatomical abnormality is not possible

Coeliac Disease

The commonest form of anaemia found in cases of coeliac disease is due to iron deficiency a true megaloblastic anaemia is generally considered to be rare the haematological features and responses are similar to those of the sprue syndrome As in sprue the deficiency is often mixed

Nutritional Megaloblastic Anaemias

It is often difficult to be certain of the nature of many examples of macrocytic anaemia reported from tropical countries In the past marrow puncture was seldom employed and the true nature of the anaemia was not determined Many patients with marked dietary deficiencies have also severe associated diarrhoea and are reported as examples of the sprue syndrome (Suarez, Spies and Suarez, 1947) Again many examples of megaloblastic anaemia of pregnancy reported from tropical areas are probably primarily due to nutritional deficiencies which have been exacerbated by the pregnancy (Chaudhuri 1951) Other factors such as iron deficiency infection and worm infestation are often also present Recent reports have shown that many of these cases respond to vitamin B_{12} (Chaudhuri 1951) though the remissions obtained are not as rapid or complete as those to be expected in cases of Addisonian megaloblastic anaemia of comparable severity very much larger doses of vitamin B_{12} are often required (Ungley 1951–2) Many of the older reports were concerned with the effects of liver extracts these were often used in inadequate quantities and the results obtained were not of much value now that pure preparations are available it is hoped that more definite information will be forthcoming It seems very likely that many of the conditions will turn out to be due to multiple deficiencies

Megaloblastic Anaemia of Pregnancy

(a) As Seen in Temperate Climates The predominant deficiency in these cases is always folic acid Occasional cases have been reported of responses to vitamin B_{12} (Lowenstein Pick and Philpott 1955) but these are usually suboptimal Many of the older reports are very confusing it is probable that the responses sometimes seen after the administration of crude liver extracts were due to folic and folinic acids which these

preparations contained How the deficiency arises is still not understood In some cases there is a very marked dietary deficiency and vomiting is severe in others the diet is excellent but in the majority of cases reported by Thompson and Ungley (1951) the diet was poor, but no worse than that of many women who did not develop megaloblastic anaemia There is some evidence suggesting that one of the contributory factors may be dietary deficiency for there is a very significant increase in the incidence of the disorder during the winter and spring months when fresh green vegetables are not readily obtainable (Thompson 1957) It used to be said that this disorder always spontaneously remitted after delivery but this is certainly not invariable for many patients become steadily worse in the puerperium Moreover the disorder is commonly diagnosed first during the puerperium, although with an increasing awareness of the clinical and haematological features of the disease it is now much more frequently diagnosed during pregnancy Patients are still occasionally seen up to four months after delivery with untreated megaloblastic anaemia of pregnancy Twin births are associated with megaloblastic anaemia much more commonly than would be expected by chance The diagnosis of the condition is by no means always easy Some patients do show an anaemia with a high MCV and with a leukopenia, but in others there may be values which suggest a hypochromic iron deficiency anaemia but the MCHC is usually high The white count unlike that of Addisonian anaemia may be high (Thompson and Ungley, 1951) It is often not possible to make a definite diagnosis on the peripheral blood picture though an apparently normochromic anaemia with a falling count during the last months of pregnancy—especially if associated with vomiting loss of appetite a sore mouth and a poor dietary history—should give rise to suspicion and the marrow should be examined As long as hyperchromic anaemia is expected this disorder will be frequently undiagnosed The response to folic acid is excellent after delivery but during pregnancy is usually suboptimal Many patients will require iron supplements in addition to folic acid The anaemia only very rarely recurs in later pregnancies and maintenance treatment is not required Achlorhydria is found quite frequently but a family history of anaemia is not found and no case has been reported to develop classical Addisonian megaloblastic anaemia later

(*b*) *In the Tropics* These cases are discussed briefly above they are probably examples of nutritional anaemia in which pregnancy is an incidental though no doubt a very important contributory factor

Megaloblastic Anaemia of Infancy

Since the report of Zuelzer and Ogden (1946) this disease has been recognized much more frequently than in the past While some cases

are due to vitamin B_{12} deficiency others respond only to folic acid or folinic acid (Sturgeon and Carpenter 1950 Ungley 1951–2) Ascorbic acid has been found to be necessary for the conversion of folic acid to the active form of folinic acid (page 264) and it is of great interest to find that some case reports mention evidence of ascorbic acid deficiency or even of frank scurvy (Aldrich and Nelson 1947) These observations link up very well with those of May and his colleagues (1950 1951 and 1952) on the production of megaloblastic anaemia in scorbutic monkeys It seems unlikely that all cases are due to one cause in most instances the aetiology is unknown Most cases occur at about three to four months of age it is very rare after the age of one when a mixed diet is taken so that dietary factors are very likely All cases will respond to folic acid but in a disorder about which so little is known in suitable cases there is some justification in first trying the effect of vitamin B_{12} and of ascorbic acid

Megaloblastic Anaemia in Association with Ascorbic acid Deficiency

As has been mentioned above there is some evidence that ascorbic acid may be required for the transformation of folic to folinic acid (Nichol and Welch 1950a) There is also experimental evidence that a megaloblastic anaemia can be produced in monkeys by dietary deficiency that the megaloblastic change is due to a defect in folic-acid metabolism and that this is related to ascorbic acid deficiency (May *et al* 1950 1951 Proehl and May 1952) These authors point out however that the diet contained only small amounts of folic acid and that adding folic acid prevented megaloblastic change during scurvy They were unable to detect any direct specific function of ascorbic acid in haematopoiesis Although there is clinical evidence that some cases of megaloblastic anaemia of infancy may be due to vitamin C deficiency (*q v*) there is very little evidence to suggest that vitamin-C deficiency alone can result in megaloblastic erythropoiesis in the adult When possible instances of megaloblastic anaemia in scurvy are collected together they do not make an impressive number even when the anaemia is macrocytic the bone marrow is almost invariably normoblastic

Associated with Tapeworm Infestation

The exact aetiology of this disorder was until recently a great mystery It is now clear however that the parasite dibothriocephalus latus when situated high in the small intestine absorbs vitamin B_{12} from the intestinal contents and utilizes it for its own growth thus interfering with the absorption of the vitamin by the host Dead worms have been shown to contain large amounts of vitamin B_{12} indeed they can be used as a source of vitamin B_{12} for the treatment of patients

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are due to vitamin B_{12} deficiency others respond only to folic acid or folinic acid (Sturgeon and Carpenter 1950 Ungley, 1951–2) Ascorbic acid has been found to be necessary for the conversion of folic acid to the active form of folinic acid (page 264) and it is of great interest to find that some case reports mention evidence of ascorbic-acid deficiency or even of frank scurvy (Aldrich and Nelson 1947) These observations link up very well with those of May and his colleagues (1950 1951 and 1952) on the production of megaloblastic anaemia in scorbutic monkeys It seems unlikely that all cases are due to one cause in most instances the aetiology is unknown Most cases occur at about three to four months of age it is very rare after the age of one when a mixed diet is taken so that dietary factors are very likely All cases will respond to folic acid but in a disorder about which so little is known in suitable cases there is some justification in first trying the effect of vitamin B_{12} and of ascorbic acid

Megaloblastic Anaemia in Association with Ascorbic acid Deficiency

As has been mentioned above there is some evidence that ascorbic acid may be required for the transformation of folic to folinic acid (Nichol and Welch 1950a) There is also experimental evidence that a megaloblastic anaemia can be produced in monkeys by dietary deficiency that the megaloblastic change is due to a defect in folic acid metabolism and that this is related to ascorbic acid deficiency (May *et al* 1950 1951 Proehl and May 1952) These authors point out however that the diet contained only small amounts of folic acid and that adding folic acid prevented megaloblastic change during scurvy They were unable to detect any direct specific function of ascorbic acid in haematopoiesis Although there is clinical evidence that some cases of megaloblastic anaemia of infancy may be due to vitamin C deficiency (*q v*) there is very little evidence to suggest that vitamin C deficiency alone can result in megaloblastic erythropoiesis in the adult When possible instances of megaloblastic anaemia in scurvy are collected together they do not make an impressive number even when the anaemia is macrocytic the bone marrow is almost invariably normoblastic

Associated with Tapeworm Infestation

The exact aetiology of this disorder was until recently a great mystery It is now clear however that the parasite dibothriocephalus latus when situated high in the small intestine absorbs vitamin B_{12} from the intestinal contents and utilizes it for its own growth thus interfering with the absorption of the vitamin by the host Dead worms have been shown to contain large amounts of vitamin B_{12} indeed they can be used as a source of vitamin B_{12} for the treatment of patients

suffering from tapeworm megaloblastic anaemia (von Bonsdorff and Gordin 1952) Patients should be treated by vermifuges and vitamin B_1 once remission of anaemia is attained there is no need for main tenance therapy It is of course necessary to distinguish cases of true Addisonian megaloblastic anaemia with incidental tapeworm infesta tion which will require maintenance treatment

Following Gastrectomy

It has been shown recently by Callender, Turnbull and Wakisaka (1954) that the secretion of intrinsic factor is often reduced after total gastrectomy to the same degree as occurs in Addisonian megaloblastic anaemia They recommend the regular administration of vitamin B_{12} to such patients Although megaloblastic anaemia after total gastrec tomy has not often been reported this may well be due to the short survival time as the operation is so commonly performed for car cinoma Megaloblastic anaemia has also been reported after partial gastrectomy and gastro enterostomy (Badenoch Evans, Richards and Witts, 1955) It was thought likely that prolonged gastritis might have been responsible for the loss of gastric secretion Steatorrhoea does occur in some patients after these operations it was not considered to be a significant factor in those reported by Badenoch *et al* (1955)

Although as would be expected vitamin B_1 is usually effective in these cases one patient required folic acid therapy in addition (Conway and Conway 1951)

In Association with Diffuse Neoplastic Infiltration of the Bone Marrow and with Leukaemia

Many of the older reports of this association are unreliable for the megaloblastic cells were diagnosed from tissue sections in which the finer points of histology of marrow cells are quite unrecognizable Patients with acute leukaemia quite commonly have an anaemia with a high MCV, in such cases there are usually many macronormoblasts present in the marrow Very primitive erythroid cells sometimes closely resembling megaloblasts are however occasionally encountered but usually in small numbers and the primary condition is usually obvious In the writer s experience these megaloblast like cells are more common in acute monocytic and myelo monocytic leukaemias than in other types At times the erythroid changes predominate many such cases have probably been reported as so called Di Guglielmo s disease The leukaemic or neoplastic cells may utilize excessive amounts of haemato poietic material for their growth and thus interfere with the normal maturation of the red cell series if this were true these patients should respond and the marrow should revert to normoblastic erythropoiesis on administration of vitamin B_1 or folic acid this is very rarely the

case (Stone 1950 and personal observations) Studies of folic acid levels in the plasma of leukaemia do however show low levels (Spray and Witts 1953) Another possible explanation is that metabolites from the neoplastic tissue interfere with cell growth

In Patients Treated with Folic acid Antagonists

In view of the importance of folic acid in haematopoiesis it would be expected that megaloblastic change would be common in patients treated with folic-acid antagonists This is observed only rarely however cells remotely resembling megaloblasts if they occur at all usually appear only in very small numbers though occasionally they are numerous and immature (Wilson 1951)

Megaloblastic Anaemia Associated with Anticonvulsant Therapy

Since 1954 some thirteen papers have appeared in which this association has been described (Gydell 1957) The anticonvulsant therapy has often been multiple and has commonly been diphenyl hydantoin or primidone together with phenobarbitone Megaloblastic anaemia has been reported following the use of diphenyl hydantoin and primidone separately it has also been described in association with a proprietary barbiturate consisting of equal parts of amylobarbitone sodium and quinalbarbitone sodium (Hobson Selwyn and Mollin 1956) The anticonvulsants have usually been taken for some years but anaemia has developed after four months of such therapy (Fuld and Moorhouse 1956) Most of the patients have been in a young age group in which Addisonian pernicious anaemia is very rare in adequately investigated patients this diagnosis has been excluded as has any evidence of malabsorption (Gydell 1957) Responses to vitamin B_1 have usually been negative or poor while folic acid has never failed to give a satisfactory remission if such treatment is maintained the anticonvulsant therapy can be maintained also Girdwood and Lenman (1956) have pointed out structural similarities between folic acid and the anticonvulsants incriminated and have suggested that the latter act as competitors in some enzyme system and so block some synthetic process requiring folic acid Why only certain patients should develop the anaemia and why there should be such a long interval between commencement of anticonvulsant treatment and onset of anaemia is not explained

So-called 'Idiopathic Refractory Anaemia'

Since folic acid became available the number of cases in which the above diagnosis is made have dwindled considerably Many of the cases diagnosed in the past as refractory anaemia or achrestic anaemia were no doubt examples of folic acid deficiency In many

instances there was probably occult steatorrhoea In other cases the marrow was not megaloblastic, there is no point in referring to such cases as refractory anaemia the diagnosis should be that of the primary condition which usually is of some well recognized disorder such as aplastic anaemia or aleukaemic leukaemia Cases of true megaloblastic anaemia which do not fall into one of the groups mentioned above are exceptional it must be remembered that several years may sometimes elapse before the diagnosis of a case of steatorrhoea becomes manifest

In Liver Disease

This is discussed above (page 246)

Evidence of Increased Red-cell Destruction in the Megaloblastic Anaemias

In certain patients suffering from megaloblastic anaemias due to deficiency of either vitamin B_1 or folic acid the circulating erythrocytes may have a shortened life span, in rare cases this may be very pronounced Using the Ashby differential agglutination technique Hamilton De Cowan Sheets, Janney and Ellis (1954) have demonstrated that fresh normal erythrocytes when transfused into patients with Addisonian megaloblastic anaemia in relapse are destroyed rapidly in a random fashion and point out that haemolysis may make a very substantial contribution to the anaemia A normal survival time for such transfused cells was found when vitamin B_1 was given nine to twelve days before transfusion the rate of destruction was greater the later vitamin B_1 was given and the fastest rate occurred in an untreated patient This destruction may be due to an inherent abnormality in the red cells themselves but the observed short survival time of transfused fresh normal cells makes it clear that there must be an extracorpuscular haemolytic mechanism also the nature of this is quite unknown Not all studies have shown this decreased survival of transfused normal erythrocytes (Mollison 1947 Singer King and Robin 1948) It is probable that only certain patients have an extracorpuscular haemolytic process certainly clinical observations would suggest that the degree of haemolysis varies greatly from patient to patient Finch Coleman, Motulsky Donohue and Reiff (1956) conclude that there is in patients with Addisonian megaloblastic anaemia an average destruction rate of the patients own erythrocytes of about three times normal At the same time, evidence marshalled by Finch and his associates (1956) suggests that the effective production of erythrocytes is about normal in Addisonian anaemia The low reticulocyte count found in Addisonian anaemia in relapse is sometimes used as evidence against the presence of a haemolytic process As pointed out by Finch *et al* (1956), one of

the characteristic features of erythropoiesis in Addisonian anaemia is the early appearance of nucleated cells By the time the nucleus is excluded the cytoplasmic reticulum has usually disappeared When N^{15} labelled glycine is administered it becomes incorporated in the porphyrin ring of haem (*q* v) the survival time of erythrocytes containing such labelled haemoglobin may be readily followed It appears that in Addisonian megaloblastic anaemia in relapse some red cells have a normal survival time whereas others are destroyed unduly rapidly and at random (London and West 1950 James III and Abbott 1953)

Related to these problems of increased red cell destruction are studies of bile pigment metabolism in Addisonian megaloblastic anaemia London and West (1950) observed a very rapid elimination of labelled bile pigment after administration of N^{15} labelled glycine to patients with Addisonian megaloblastic anaemia in relapse This elimination was so rapid as to preclude an origin from the haemoglobin of mature circulating erythrocytes There are two possible explanations for this observation one is that there is a breakdown of very newly formed red cells in the marrow before they ever reach the circulation the other is that such labelled bile pigment may have originated directly from labelled porphyrins which were never incorporated in erythrocytes at all That such quantities of pigment could have arisen from the destruction of other haem pigments such as myoglobin seems most unlikely Whether bile pigment can be formed directly from pyrroles and pyrrole precursors without the formation of a porphyrin ring structure is unknown

It seems very likely that there is in fact an excessive destruction of young cells in Addisonian megaloblastic anaemia in relapse though how this comes about is unknown After discovery of the efficacy of liver treatment it became almost heresy to regard pernicious anaemia as other than a deficiency disease though before that time it had always been classified as a haemolytic anaemia It is now apparent that haemolytic and indeed perhaps other factors sometimes play a very prominent part

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ABNORMALITIES OF THE HAEMATOPOIETIC SYSTEM ASSOCIATED WITH ENDOCRINE DYSFUNCTION

Hypothyroidism

Anaemia which responds to thyroid therapy frequently develops as a direct result of deprivation of the thyroid hormone It must be remembered however that anaemia due to iron or vitamin B_{12} lack may be

associated with though as far as is known not in any way due to hypothyroidism The response of such an iron or vitamin B_{12} deficiency anaemia to specific therapy will be modified by the associated thyroid deficiency complete remission will also require correction of the hypo thyroid state

The true anaemia of hypothyroidism may be normochromic and normocytic but is frequently macrocytic in neither instance is it usually severe In the macrocytic variety the peripheral blood shows only a moderate and uniform macrocytosis anisocytosis and poikilocytosis are not found The bone marrow is hypoplastic (Bomford 1938 Jones 1940) megaloblasts do not occur there is no evidence of vitamin B_1 or folic acid deficiency and the anaemia does not respond to these substances In rare instances severe aplasia may be found with sclerosis of the thyroid gland (Jaffe 1938) While 53 % of Lerman and Mean s (1932) patients had achlorhydria this is not related to the aetiology of the anaemia except that it may play a part in accelerating the development of iron deficiency if other factors tending towards this are present

A reduced blood volume is said to be common in myxoedema (Thompson 1925–6 Chang 1931) It is stated that the volume may rise by 25 / or more after thyroid treatment (Thompson 1925–6) A rise in plasma volume without a coincident rise in red cell volume accounts for the frequently observed initial fall in the haematocrit immediately after beginning thyroid treatment Carotenaemia is commonly present in myxoedema (Bomford 1938) the yellow colour which it produces in the skin may suggest icterus and lead to a clinical diagnosis of pernicious anaemia Such an error will be more readily made if the anaemia is of the macrocytic type

After thyroid treatment there is no reticulocytosis and regeneration of blood is slow complete remission of anaemia may take several months The response is quite unlike that seen after specific treatment has been given to a patient suffering from vitamin B_1 folic acid or iron deficiency There is nothing to suggest that thyroid hormone is a specific haemopoietic substance (Bomford 1938) the anaemia of myxoedema is probably due to a general depression of metabolism

Hyperthyroidism

In hyperthyroidism there is but little significant change in the blood The white cell count is usually low or normal and a relative granu locytopenia with lymphocytosis is commonly found this lymphocytosis has not however the diagnostic importance originally ascribed to it by Kocher (1908) Bistrom (1946) correlates the lymphocytic infiltration of the thryoid with the degree of lymphocytosis It is natural that the present theory of the cause of the general hypertrophy of lymphoid

tissue and the lymphocytosis should be related to an associated or relative deficiency of adrenal steroids (Selye 1937)

Thymus

Ross, Finch, Street and Strieder (1954) report two personal cases in which there was an association between benign thymoma and a refractory anaemia Seven similar cases were collected from the literature two patients had myasthenia gravis In three of these ten patients thymectomy resulted in a marked clinical improvement The authors discuss the possible relationships between the two disorders, it would certainly seem well worth while to investigate this matter further for the evidence is at present very scanty

Addison's Disease

The blood picture in 100 patients with Addison s disease has been reviewed by Baez Villasenor Rath and Finch (1948) They point out the difficulty of assessing haematological values in untreated patients owing to haemoconcentration, some patients showing an elevation of haemoglobin, as do experimental animals in a crisis (Corey and Britton 1932) There may also be changes in red cell volume due to change in osmolar concentrations of intra and extracellular fluid, these changes are unlikely to be great as following treatment there is a parallel fall in values for packed cell volume haemoglobin and red-cell count Baez Villasenor *et al* (1948) state that they can assume a 20% drop in haemoglobin level following treatment there may be a subsequent rise suggesting that the drop in the relative concentration of haemoglobin has acted as a stimulus to haematopoiesis A slight normochromic normocytic anaemia is common in Addison s disease In a group of stabilized patients the average haemoglobin was 13 5 g In four patients radioactive iron studies showed that iron utilization for haemoglobin formation was very slightly less than normal Leucocyte changes were most prominent in the group receiving maintenance treatment by DOCA or adrenal-cortical extract (Baez Villasenor *et al* 1948) this is considered to be accounted for by a longer duration of hypoadrenalism In this group leukopenia of under 5000 per cu mm was found in 21% of patients while lymphocytosis and neutropenia was found in about 50% Such changes together with a general increase in lymphoid tissue have for long been recognized as a feature of Addison s disease (Rowntree and Snell 1931) Eosinophilia is uncommon and of no diagnostic value The blood picture was not significantly different in those cases due to tuberculosis and those due to adrenal atrophy Large doses of DOCA and maintenance doses of adrenal extract have no influence on the blood picture apart from those changes associated with correction of haemoconcentration only

ortisone and related substances will correct the cellular changes Thorn Forsham and Emerson 1949)

Cushing's Syndrome

Polycythaemia is often quoted as being common in Cushing s syndrome and it was emphasized in the original description (Cushing 932) The florid appearance of the patient often leads to a clinical diagnosis of polycythaemia but in about half of the cases the red-cell ount is normal (Thompson and Eisenhardt 1943 Plotz Knowlton and Ragan 1952) the highest count met with by the latter authors was 6 9 million The polycythaemia does not appear to lead to any of he complications associated with polycythaemia vera In one series he eosinophil count was below 100 per cu mm in 79% of cases

Gonads

There is a well established sex difference in red cell count and haemoglobin values those in the male being higher than those in the emale this holds not only for man but also for mammals and birds This sex difference may be annulled by male castration and restored by testosterone Eunuchoid men have slightly subnormal red cell counts which become normal on testosterone therapy and relapse on cessation of treatment (McCullagh and Jones 1942) Ovariectomy in rats causes a rise in the red cell count and haemoglobin to nearly the levels maintained by castrated males and the administration of oestradiol to these animals restores their blood values to those of the normal female The influence of oestrogens is difficult to assess in the experimental animal for great specie variations exist and the doses used are often unphysiological Probably the sex hormones influence haematopoiesis purely by their general metabolic effects the matter is more fully discussed by Daughaday Williams and Daland (1948)

The Pituitary

Anaemia has been frequently observed to follow destruction of the pituitary in man and in animals If the precise cause of anaemia developing in association with deficiency of individual endocrine glands under pituitary control is obscure this is even more true when the pituitary is itself primarily involved Van Dyke Garcia Simpson Huff Contopoulos and Evans (1952) have by hypophysectomy in the rat related the anaemia to removal of the anterior lobe extirpation of the intermediate and posterior lobes did not change the haemoglobin concentration haematocrit or volume of circulating red cells Sometimes in hypopituitarism one gland seems predominantly affected thus in some patients the clinical picture is principally one of hypothyroidism The clinical impression is often of a more severe anaemia than is actually

present While patients with hypopituitarism may maintain relatively normal red-cell counts but rather low haemoglobin concentrations at first there is a tendency for anaemia to develop some years later Occasionally red-cell counts of 2–3 million are met with (Sheehan 1937 and 1939) A macrocytic anaemia has been described this may be due to hypothyroidism (*q v*) In two thirds of Sheehan s 1939 cases there was a relative lymphocytosis and a moderate eosinophilia Escamilla and Lisser (1945) in 101 cases of pathologically verified Simmond s disease found a mean haemoglobin of 65% (range 40–102%) and a mean red cell count of 3 7 million (range 2 0–5 6 million) They also noted an eosinophilia (mean 6 5%) as a common finding the same comment is made by Silver (1933) whose haemato logical findings are very similar Snapper Groen Hunter and Witts (1937) and Witts (1942) tend to stress the influence of achlorhydria and malabsorption and relate the aetiology of the anaemia to pernicious anaemia This is a subject in need of further investigation by some of the more recently developed techniques such as tests of radioactive vitamin B_{12} absorption After hypophysectomy the bone marrow is hypo plastic (Crafts 1946) The anaemia of hypopituitarism as commonly encountered is probably the result of a depression of general metabolism and is not due to the absence of any specific haematopoietic factor

Androgens have proved partially effective in treatment of the anaemia of hypophysectomized male rats, Crafts (1952) found that the only treatment which maintained a normal red cell level was a combination of a high protein diet with thyroxine and testosterone propionate In contrast cobalt intake had a profound effect on the haemoglobin as well as on the erythrocyte count Haematological improvement in the anaemia of hypopituitarism is difficult to attain and maintain *though some clinical improvement may result from endocrine therapy* The use of anterior pituitary hormones is as yet unsatisfactory thyroid and testosterone appear to be the most valuable endocrine preparations for use in this disorder and cortisone has also been shown to be effective An adequate protein intake is indicated and cobalt therapy is certainly worth a trial

The Effect of Adrenocortical Steroids and ACTH on Haematopoiesis

In a great variety of disease states many of the inflammatory or immunological type administration of cortisone or ACTH besides producing clinical improvement induces a reticulocytosis and improve ment of associated anaemia (Finch Crockett Ross and Bayles 1951) Why this should occur is unknown as is the reason for the reticulo cytosis which can be produced by these substances in pernicious anaemia (Thorn Forsham Frawley, Hill Roche Staehelin and Wilson

1950) There is no report of polycythaemia even after prolonged treatment with these steroids in very high dosage In both man and animals cortisone and ACTH produce a very marked neutrophilia (Sprague *et al* 1950 Finch *et al* 1951 Quittner Wald Susman and Antopol 1951) An adverse effect might be expected in acute or sub acute myeloid and monocytic leukaemia and this is sometimes observed (Fessas Wintrobe Thompson and Cartwright 1954 Thompson 1957) A case of reticulum-cell sarcoma terminating in rapidly fatal monocytic leukaemia after cortisone administration has been reported

A fall of eosinophils is the most striking manifestation in the peri pheral blood its degree probably depends on the level of steroid in the blood stream The cause of this dramatic fall is unknown There may be an inhibition of production or of release of eosinophils from the marrow or they may be segregated or destroyed This matter is as yet unsettled a discussion may be found in reviews by Thorn (1953) and Esseller Jeanneret and Morandi (1954) A further very pronounced effect is a depression of all lymphoid tissue both normal tissue and the abnormal cells of acute and chronic lymphatic leukaemia and lympho sarcoma are affected The action of the steroids is not only depressant there is much evidence of actual cell destruction (Feldman 1950 Heilman 1945) There is a great mass of data much of it unsatisfactory and very controversial on the relationship of the cytolytic changes produced in lymphoid tissue to the liberation of antibodies (Valentine Craddock and Lawrence 1948) The dissolution of lymphoid tissue mediated by adrenal cortical hormone under control of the neuro hypophysis has been considered by many authors to be part of the normal defence mechanism of the body against infection (Dougherty and White 1945 White and Dougherty 1945) It seems unlikely that many of the gross changes which have been demonstrated in laboratory animals have any relation to those occurring in man either under physiological conditions or as part of the normal defence mechanism It does appear probable that the adrenal cortical steroids have a very important influence on lymphoid tissue and that this may be exerted during the response to stress of various kinds

In idiopathic thrombocytopenic purpura and in symptomatic thrombocytopenia associated with a megakaryocyte rich marrow cortisone and ACTH are often of great therapeutic value as a temporary measure either while preparing for splenectomy when indicated or to cover the natural course of the disease in the acute symptomatic type of thrombocytopenia Finch *et al* (1951) have demonstrated no effect on normal platelets and cortisone and ACTH are ineffective in thrombo cytopenic states associated with marrow aplasia

"Haemopoietine"

This name was given by Carnot and Deflandre (1906) to a hypothetical blood borne substance believed to stimulate and regulate erythroid bone marrow *It is clear that a very sensitive control mechanism* must exist for all formed elements of the blood, but its nature is unknown, conclusive proof even of its existence is lacking Van Dyke *et al* (1954), in a valuable review of the subject present evidence that the anterior pituitary plays an important direct role in the control of circulating red cell volume No other known endocrine glands seem to be implicated the thyroid adrenals and testes seem to influence haematopoiesis solely by their general metabolic effects

Production of anoxic or anaemic anoxia are the methods which *have been most extensively used for the experimental stimulation* of erythropoiesis and for attempts to demonstrate a haemopoietine Other workers have tried to prepare plasma extracts from bled rabbits and to demonstrate an erythropoietic effect on injecting such extracts into normal animals (Borsook Graybiel Keighley and Windsor, 1954 Gordon Tanenbaum and Siegal 1955) The extracts obtained by this method have not been of high potency Much more active extracts have been prepared from phenylhydrazine treated animals especially those with liver damage and it is suggested that the damaged liver is *unable to destroy the active substance* (Jacobson Davis and Alpen 1956) Reissman (1950) kept one of a pair of parabiotic rats anoxic while the other breathed room air A polycythaemic response occurred in both animals, the percentage of erythroid elements in the marrow increased with the degree of polycythaemia The transmission of a substance stimulating erythropoiesis from the anoxic rat to its partner seems very probable Grant (1952) has further shown that mice and rats suckled from anoxic mothers developed higher red-cell counts and total body haemoglobin levels than control animals suckled from mothers breathing room air The evidence is very suggestive a humoral mechanism for the control of erythropoiesis seems very probable and such a hypothesis provides a useful working basis for further experiment All the older evidence bearing on this subject is very fully reviewed by Grant and Root (1952)

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CHAPTER 13

DISTURBANCES OF METABOLISM AFFECTING THE CENTRAL NERVOUS SYSTEM

J D SPILLANE

GENERAL CONSIDERATIONS

THE nervous system functions by virtue of the activity of innumerable nerve cells The preservation of consciousness mental processes movement the exercise of the senses and the regulation of autonomic activity are possible only on the basis of an adequate supply of energy The neurosurgeon exposing the living brain reveals the signs of this activity—the warmth the pulsation the changing tint of the circulating blood—and he may explore and record the electrical activity of the cortex and deeper structures The neurophysiologist demonstrates that a vital alteration of electrical action potential takes only a fraction of a second to complete while the neurochemist can measure the simultaneous change in the distribution of sodium and potassium ions But we know little of the chemical processes which underly this ceaseless activity

The Cerebral Circulation

The transport of the essential glucose and oxygen to the brain is accomplished by the paired carotid and vertebral arteries major branches of which fuse at the base of the brain to form the anastomosis of the Circle of Willis This structural arrangement has presumably evolved in man so that an adequate flow of blood to the brain is ensured Within the substance of the brain there are no arterial anastomoses In some species of animals the vertebral or the carotid system is insignificant in the common laboratory animals and in man both systems are important In the brain as in other organs of the body functional activity oxygen uptake and blood flow are intimately related Cerebral metabolic activity will be reduced when there is substrate insufficiency as a result of a primary anoxia or hypoglycaemia or of failure of the circulation It can also be impaired as a result of disturbance of intermediary metabolism The vascularity of the brain varies in different parts and there probably are intrinsic mechanisms which influence local and general blood flow Whereas there are a large variety of substances of which CO_2 is the most potent which are capable of dilating cerebral

arteries and increasing the blood flow vasoconstrictor agents are few Oxygen possesses moderate vasoconstrictor properties Vasodilatation in the brain may be brought about by the activity of metabolic products or vasomotor nerves The latter may respond to activation by the stimulus responsible for the increased neuronal activity or through locally placed chemoreceptors

The rate of cerebral blood flow ultimately depends on the pressure head at the level of the cranium and on cerebrovascular resistance Although there must obviously be a critical level of blood pressure below which cerebral circulation is inevitably reduced the main regulator of cerebral blood flow in normal circumstances is the resistance encountered within the cranium The intracranial pressure the viscosity of the blood and the state of the cerebral vessels largely determine the degree and location of this resistance Drugs have only transient effects on the cerebral blood vessels in man and there is little evidence that vascular tone is an important factor in the normal regulation of blood flow in the brain

The diffusion of substances from the blood into the brain and cerebrospinal fluid is a complex and dynamic process The idea of a physical blood brain barrier grew out of the observations of Ehrlich in 1885 that aniline dyes injected into the blood stream stained all tissues of the body except those of the nervous system No anatomical barrier can be identified and it is now considered that the permeability of the vascular endothelium and of the nerve-cell membrane together with the ability of nervous tissue to select or reject substances all take part in the formation of the barrier system

Until recently quantitative studies of the cerebral circulation in man were not possible Observations of the retinal circulation and of the effects of occlusion of the internal jugular veins on the displacement of cerebrospinal fluid were not very helpful Determination of the cerebral arterial venous oxygen difference by analysis of samples of carotid and jugular blood for their gaseous exchange has been widely used (Lennox and Gibbs 1932 Loman and Myerson 1936) Experience has shown that the cerebral A V oxygen difference being the product of the interrelation between cerebral blood flow and cerebral metabolisms cannot itself be a measure of either (Schmidt 1950) Kety (1948) has devised a method of quantitative measurement of the cerebral blood flow and cerebral metabolism in intact man by applying the familiar Fick principle This states that the quantity of a given substance taken up by an organ in a given time from the arterial-blood equals the amount of the substance carried to the organ by the arterial blood *minus* the amount removed by the venous blood during the same time The substance normally used is nitrous oxide as it is readily introduced into the blood stream by inhalation and is freely diffusible and easily measured Blood

samples are collected simultaneously from an artery and the superior jugular bulb at intervals during and after the inhalation of this gas Himwich (1951) calculates the Cerebral Metabolic Rate (CMR) according to the formula CMR = A V oxygen difference × cerebral blood flow per minute He finds that the CMR is depressed by deprivation of oxygen or glucose and by such diseases as cerebral arteriosclerosis organic psychoses and in coma of all kinds The CMR is raised by the administration of the deficient substrate (glucose or oxygen) or in the case of thiamine deficiency by restoring normal intermediary metabolism by the administration of thiamine Irreversible brain damage is associated with the lowest recorded CMRs

Approximately 15 / of the blood pumped to the body by the heart goes to the human brain It has been calculated (Ferris Engel Stevens and Logan 1946 Gibbs Maxwell and Gibbs 1947) that in normal adults the rate of cerebral blood flow is about 600 ml /min but under varying physiological conditions it can range between 300 and 1300 ml /min The brain s oxygen consumption is such that in adults at rest the brain takes up about one quarter of the total oxygen used by the body Although alterations of posture exercise or breathing may appreciably influence the cerebral circulation the cerebral respiratory rate remains stable It has been estimated (Kety 1955) that there are 5 ml of oxygen in the cerebral blood and 2 ml dissolved in the brain substance itself at any one time At a normal rate of oxygen utilization of 46 ml /min this total of 7 ml would last about ten seconds

Chemical Constitution of Brain

It is obvious that this relatively high rate of cerebral metabolic activity must be associated with changes in the constituents of the brain itself Brain is made up approximately of water 78% lipids 10 / protein 8 / soluble organic substances 2% inorganic salts 1% and carbohydrate 1 / (McIlwain 1955) Yet more is known of the cerebral metabolism of carbohydrates than of lipids or proteins Actual chemical analysis of normal brain tissue began with the work of Thudichum (1829–1901) It did not as one might have expected wait upon the classical discoveries of clinical and experimental neurology at the turn of the century Thudichum s classic *A Treatise on the Chemical Constitution of the Brain* was first published in 1884 He was a German exile who became a British subject and who practised in London as an aural surgeon he also became Professor of Pathological Chemistry at St Thomas s Hospital His pioneer researches were carried out in his capacity as chemist to the Medical Department of the Privy Council He used more than one thousand human and animal brains and described named and classified many cerebral lipids (cephalins cerebrosides and sphingomyelins)

The techniques which have been adopted to study changes in brain tissue under varying conditions comprise the analysis of brain specimens after rapid fixation by liquid air, the assessment of the ability of different foodstuffs to support the metabolism of excised cerebral tissue and the study of labelled metabolites The investigation of the cerebral consequences of anoxia, anaesthesia, convulsions and hypoglycaemia have also yielded information of a fundamental character

Carbohydrates The addition of various substances to the fluid in which brain slices are suspended has demonstrated that only glucose lactic acid and pyruvic acid are effective in maintaining tissue respiration *In vivo* only glucose is effective and in the hepatectomized animal life can be prolonged only by maintaining cerebral metabolism by the administration of glucose or glucose producing substances (mannose maltose) The Respiratory Quotient (the ratio of the volume of CO_2 produced to the volume of O_2 consumed) obtained by analysing inspired and expired air is known for different foodstuffs (fat 0 7 protein 0 8 carbohydrate 1 0) For the intact brain and also for excised brain slices the RQ is 1 in man and certain animals Lastly, it has been shown that the oxidation of glucose accounts for the greatest part of the O_2 intake Carbohydrates are therefore the normal source of brain energy oxidation of fats does not apparently take place in the brain

Ingested carbohydrates are split by enzymes into hexoses and are absorbed into the blood stream and conveyed to such tissues as brain liver muscles and kidneys If not required for immediate oxidation they are converted to glycogen and stored in liver and muscle Brain contains a small store (2 g) of glucose and glycogen which remain relatively unaffected by external influences so that hypoglycaemia is of less immediate danger than anoxia Brain glycogen is probably able to sustain cerebral metabolism for ninety minutes at the low level present in hypoglycaemia coma Rapid release of liver glycogen in the form of glucose is facilitated by the liver enzyme phosphatase The availability of glucose is therefore of cardinal importance to the brain and the blood sugar level itself is under endocrine (islet cell adrenal anterior pituitary) and neural (autonomic) control Insulin the only hormone which lowers blood sugar increases the rate of carbohydrate oxidation Although the brain has to rely on glucose it is able to oxidize it without the aid of insulin—fortunately for the diabetic Anterior pituitary and adrenal cortical activity slows carbohydrate oxidation by depressing the vital glucokinase reaction (i e phosphorylation) and limiting the utilization of glucose by non nervous tissues On the autonomic side it had always been considered that the restoration of normal blood sugar level after hypoglycaemia is effected by means of adrenaline It has now been shown however that this restoration is not delayed by reducing sympathetic activity by means of ganglion blocking agents

(Billington Paton Reynolds and Sherlock 1954) or by surgical sym pathectomy (French and Kilpatrick 1955) Adrenalectomy likewise does not interfere with this process of restoring the blood sugar to normal level (Ginsburg and Paton 1956) so that the responsible neurohumoral controlling mechanism does not depend on adrenaline

The methods adopted by the brain for the utilization of glucose are fundamentally the same as those of other tissues but it is possible that the brain also makes use of other methods Energy is obtained by degradation of carbohydrate by the Emden Meyerhof path to form pyruvate and then by the oxidation of pyruvate to CO_2 and water The second path is by means of the Krebs cycle (tricarboxylic acid cycle) and requires the presence of diphosphothiamine (vitamin B_1) That there must be some other method of carbohydrate oxidation in brain seems to be indicated by the observation that inhibition of either the degradation of carbohydrate or the oxidation of pyruvate does not necessarily depress the cerebral oxidation of glucose (Himwich 1951) It is not known why products of intermediate carbohydrate metabolism such as pyruvate are ineffective in controlling the symptoms of hypoglycaemia

Lipids Less is known of the metabolism of neural lipids than of their chemistry Abnormalities occur in the so called demyelinating dis orders and in the lipidoses (page 311) Brain differs from most other tissues in that its proportion of neutral fat is lower and that of total lipids and cholesterol cerebrosides and sphingomyelins is higher Growth of brain and nerve is accompanied by an accumulation of lipid but in the adult brain the content of lipids remains presumably in a state of dynamic equilibrium remarkably uninfluenced by external changes In starvation the body may be depleted of fat but the brain retains its lipids It is possible that metabolism of these lipids is con cerned in the transport of ions across nerve cell and nerve fibre mem branes and in the steady flow distalwards along nerve fibres (Sloane Stanley 1952) Isotope studies certainly indicate that the lipids of the nervous system are in a state of active turnover

Phosphates and Nucleotides Compounds containing energy rich bonds (e g phosphates and adenine nucleotides) are important in the processes of carbohydrate oxidation in non nervous tissues and may play a similar role in cerebral metabolism (Coxon 1952) Brain con tains as much creatine phosphate and adenosine triphosphate as other tissues It is now established that energy rich phosphate bonds are formed during the process of oxidative phosphorylation The participa tion of these energy rich compounds may constitute a link between the combustion of carbohydrate and the provision of energy for the activity of the nervous system

The content of these substances in the brain of a laboratory animal is

affected by cerebral activity In states of depression or excitement of the nervous system there are large opposed changes in the brain content of phosphate containing substances Thus in sleep or narcosis creatine phosphate rises and inorganic phosphate falls in convulsions the reverse changes take place When the cerebral activity is prolonged it is the nucleotides and not the phosphates which are depleted Very little is known of the effect of diseases of the nervous system on these substances but their importance was established when it was found that their synthesis was prevented by deficiency of the vitamin B complex (McIlwain 1952)

Glutamic Acid Glutamic acid is not one of the essential amino acids but it is present in high concentration in brain tissue and it is freely assimilated and metabolized by brain (Quastel and Wheatley, 1932) It may therefore have some special function although this is not known It is readily available in the average human diet and is synthesized in human tissues Deficiency states are therefore unlikely to arise As it normally does not easily penetrate the blood brain barrier it is probable that glutamic acid does not act directly on brain cells Its beneficial effect in hypoglycaemic coma is shared by other amino acids but it is not clear by what mechanism this is achieved Walshe has observed increased glutamine in the cerebrospinal fluid in hepatic coma (1951) and a favourable response to the administration of glutamate (1953) It is said to be concerned in the enzymic synthesis of acetyl choline (Nachmansohn and Machado 1943) Although there has been little confirmation of the latter observation or of claims for its therapeutic value in petit mal and mental deficiency and while its function is not likely to be that of an energy supplying fuel (Weil Malherbe 1952) glutamic acid may nevertheless play an important role in cerebral metabolism and its study has served to re emphasize the problem of amino acid metabolism of brain tissue

Brain Metabolism and Cerebral Function

For a full discussion of this subject the reader is referred to the writings of McIlwain (1950 1952 and 1955) and Richter (1950a and b 1952) in Britain and to those of Himwich in America (1951) Volume 32 (1953) of the Research Publications of the Association for Research in Nervous and Mental Disease and *Neurochemistry* (1955) edited by Elliott Page and Quastel and the monograph by Korey and Nurnberger (1956) provide modern accounts of our knowledge of normal and abnormal metabolism within the nervous system

Striking biochemical changes occur in the brain of the experimental animal subjected to the two extremes of convulsion and anaesthesia

Convulsions induced by chemical or electrical means produce a rise in brain temperature acceleration of the cerebral circulation increased

O_2 uptake and increased electrical activity By rapidly freezing the brains of such animals with liquid air determination of metabolites can be made By such means Richter and others have been able to demonstrate that in convulsions there is increased utilization of O_2 and glucose and accelerated breakdown of high energy phosphate esters Brain tissue then contains less glycogen glucose adenosine triphosphate (ATP) and phosphocreatine and more inorganic phosphate adenosine diphosphate (ADP) and lactic acid Potassium ions pass out of the nerve cells into the interstitial fluid of the cerebral cortex and the concentration of sodium in the nerve cells is increased—an electrolyte redistribution similar to that which occurs on stimulation of peripheral nerve Convulsions also reduce the amount of acetylcholine in brain tissue In tissue slices prepared from human epileptogenic cerebral cortex Tower (1955) found impairment of acetylcholine binding metabolic loss of glutamic acid and failure to maintain tissue potassium concentrations Elliott (1955) suggests that although during an epileptic attack there are changes in oxidative metabolism and energy transfer in the brain they do not appear to be related to initiation of the seizure but to its maintenance and recovery Nevertheless it seems that a biochemical lesion does in fact exist in human epileptogenic cortex

In anaesthesia there is a decrease in cerebral metabolism this could be the cause or the result of impaired neuronal activity The accompanying biochemical changes in the brain are generally the reverse of those found in convulsions and Richter concludes that the picture is not one of exhaustion but of failure to utilize the available sources of energy Narcotics may act not by inhibiting cerebral oxidation but at a synaptic level by restricting the spread of impulses In physiological sleep although the temperature and electrical activity of the brain are reduced the cerebral circulation and oxygen consumption are not significantly lowered The acetylcholine content of the brain is higher in the sleeping animal and lower in animals which have been excited

Presumably these biochemical changes occurring in the brain under different conditions vary from one site to another Himwich suggests that the progressive impairment of brain function in anoxia hypoglycaemia and narcosis is a reflection of the Hughlings Jackson hypothesis of dissolution from the highest level which Jackson considered to occur in alcoholic intoxication The phylogenetically newer regions with their higher metabolic rates are more susceptible to environmental changes and suffer first

Little is known of the ways in which energy derived from these metabolic processes in nervous tissue is utilized physiologically The propagation of an impulse along a nerve is quantitatively associated with the movement of ions across its surface membranes In brain tissue slices it has been shown that these ionic exchanges require energy yielding

substrate including the degradation of carbohydrate The propagation of the nerve impulse is also associated with changes in specific organic constituents such as acetylcholine Resynthesis of acetylcholine is in turn dependent on energy yielding reactions (Hodgkin 1950) Nervous tissue must therefore be endlessly engaged in synthesizing substances necessary for the maintenance of its structure and functions All the evidence indicates that in the neurone we have a cell body infinitely more complex—structurally and chemically—than other cells of the human body Within these unique cells must take place much of the rapid and complicated metabolic exchange which underlies all nervous activity Biochemical processes within these neurones may conceivably vary as widely as does the morphology of the neurones themselves Localization of function in the brain may mean metabolic specialization the enzymic pattern of the cortex need not be uniform The observations of Robins and Smith (1953) that there are significant chemical differences within the cellular layers of the cerebellar cortex are of great interest in this connection

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NUTRITIONAL DISORDERS

Normal metabolic and functional activity of the nervous system depends as we have seen on an adequate supply of oxygen carbohydrate substrate and various enzyme and co enzyme systems Some vitamins for example thiamine are closely related to certain enzymes and the latter may be considerably reduced in deficiency diseases Inadequate diet and defective absorption of foodstuffs do not figure in the aetiology of the commoner disturbances of the nervous system which characterize neurological practice in a temperate climate Yet it is quite clear that vitamin deficiency *can* produce enzymatic changes in the nervous system which manifest themselves in striking neurological syndromes It was the study of a neurological malady—*beriberi polyneuritis*—which led to the discovery of vitamin B and gave such impetus to the search for accessory food substances Then there is *pellagra* a deficiency disease mainly of nicotinic acid in which the nervous system may be affected in several ways In warm climates in different parts of the world various neurological syndromes have been observed in mal nourished people during the past half-century or more During the late

war as the result of privation and disease in detention camps in the Far East and Middle East, and in the Spanish Civil War (1936-39) evidence was forthcoming that malnutrition can seriously impair the function of the nervous system Lastly there is the evidence obtained in the experimental laboratory In addition to thiamine which is essential, several members of the vitamin B_2 complex—riboflavine nicotinic acid pyridoxine pantothenic acid and vitamin B_{12}—appear to be concerned with normal function of the nervous system in certain species of animals

It is now well known of course that defective nutrition of the nervous system, as of other tissues of the body may arise in spite of a normal dietary Secondary vitamin deficiency may result from increased utiliza tion, defective absorption from the intestine as a result of disease or following intestinal operations from interference with the normal bio-synthesis of vitamins in the alimentary tract or from inactivation of vitamins in food by anti vitamin substances Examples of the latter are afforded by the Chastek paralysis of foxes when fed on raw fish which contains a thiamine splitting enzyme and by staggers the paralysis and ataxia shown by horses and cattle when bracken which also contains a thiamine splitting enzyme is included in their diet *It is also reported that certain fish products intended for human con* sumption contain thiaminase which destroys thiamine (Melnick Hochberg and Oser 1945) Lastly the development of a vitamin deficiency may be related to individual or racial peculiarities to ab-normal dietary habits or to co-existent infection and toxaemia No one has explained the striking difference between the effects of starvation observed in European and Far Eastern prison camps during the recent war In Europe the remarkable nutritional neuropathies—beriberi pellagra Wernicke s encephalopathy amblyopia nerve deafness spinal ataxia burning feet the spastic syndrome—of the Far East camps did not occur Instead we had uniform reports from many *European countries of anaemia and oedema* with slight hypoprotein aemia unexplained diarrhoea and polyuria and extremely little evidence of vitamin deficiencies It is possible that co existing infections as well as different starvation diets may be responsible for these different consequences

Deficiencies or abnormal metabolism of substances other than vita mins and enzymes may be responsible for disease of the nervous system We have in the *essential element group* the example of sway back the severe demyelination of the nervous system in new born lambs born of mothers nurtured on copper deficient pasture Among the *essential amino acids* we have phenylalanine in normal people an essential constituent of diet a derivative of which phenylpyruvic acid is improperly oxidized in that type of mental deficiency termed phenyl

pyruvic oligophrenia A low phenylalanine intake is reported to be beneficial (Bickel Gerrard and Hickmans 1953) in this disease Another type of inherited mental defect is associated with a defect in the metabolism of galactose (Holzel Komrower and Wilson 1952)

A nutritional disorder of the nervous system may arise because of maternal deficiency of some substance It has recently been shown that hydrocephalus in young rabbits can be brought about by deficiency of vitamin A in the mother during pregnancy and for fourteen weeks before mating (Millen Woollam and Lamming 1953) Stenosis of the aqueduct was at first thought to be the explanation but further studies indicated that over production of cerebrospinal fluid was responsible (Millen *et al* 1954)

It is by consideration of these and other factors in relation to nutritional deficiency of the nervous system that the complexity of the subject is appreciated Certainly in ordinary times in temperate climates disease of the nervous system is unlikely to result from dietary deficiency Nutritional disturbance is likely to come about in a less direct manner The processes by which carbohydrate is split down to provide energy for the nervous system form a complex chain of events involving the activity of many enzyme and co-enzyme systems Breakdown may occur at many points but our knowledge of such matters is scant indeed However the classic researches of Peters and his school have demonstrated one type of fundamental metabolic abnormality of the nervous system which results from nutritional deficiency

Thiamine (Aneurin)

In vitamin B_1 deficiency there is a biochemical abnormality in the nerve cells which consists of a failure in the normal oxidative metabolism of the pyruvic acid formed during the breakdown of glucose Thiamine pyrophosphate is a co-enzyme essential for pyruvate oxidation when it is absent or inactivated oxidation is incomplete conversion of pyruvate to acetyl coenzyme A fails pyruvate accumulates and the nerve cells are deprived of their normal source of energy Experimental thiamine deficiency in man and animals and *in vitro* experiments with brain tissue have proved this beyond doubt clinical confirmation is provided by studies of acute beriberi and Wernicke s encephalopathy The common biochemical fault in these two diseases which can be rapidly corrected by the administration of thiamine brings them into aetiological relationship—a fact which purely clinical considerations failed to suggest It is not known whether the subsequent degeneration of the neurones is due to intoxication by pyruvate or to failure in the supply of energy A point of clinical interest is that mild abnormalities of pyruvate metabolism may escape detection if reliance is placed on a single fasting value of the blood pyruvic acid Only after a loading dose

of carbohydrate (pyruvate tolerance test) are such abnormalities revealed (Joiner Thompson and Watson 1950)

The content of thiamine in brain tissue fluctuates less than that in other tissues of the body subjected to varying levels of dietary intake of the vitamin This stability of cerebral thiamine is presumably an indication of its importance in cerebral metabolism and may explain the difference between the clinical picture of chronic (beriberi) and acute (Wernicke s encephalopathy) deficiency of the vitamin

Inhibition of pyruvate oxidation can come about in other ways it is not necessarily due to any deficiency or interference with the mode of activity of thiamine Heavy metals such as arsenic mercury and copper and probably certain organic compounds can disturb the protein component of the pyruvate enzyme system Pyruvate accumulates and the nerve cells are deprived of a supply of energy with resulting peripheral neuropathy Thus the old clinical observation of the resemblance between arsenical polyneuritis and beriberi polyneuritis is borne out by the discovery of the similarity in the underlying biochemical lesion

Inhibition of the pyruvate oxidase system by heavy metals can be prevented and to some extent reversed by the activity of a competing dithiol 2 3-dimercaptopropropanol (BAL) (Peters Stocken and Thompson, 1945) Various forms of polyneuritis have been reported as successfully treated with BAL

These discoveries of blocks in intermediary metabolism are of the utmost importance because together with other similar observations they may provide links between certain apparently unrelated diseases of the nervous system The aetiology of other diseases, not necessarily of the nervous system may also be explained Thus Sarkar (1948) has shown that in epidemic dropsy a disease often confused with wet beri beri there is inhibition of the brain pyruvate oxidase system which results from the ingestion of a toxic alkaloid sanguinarine

The peripheral neuropathies may now be classified according to the presence or absence of normal pyruvate metabolism Thompson (1952 1955) classifies them into three main groups

(1) A type in which no [illegible] of pyruvate [illegible] detected so that th[illegible] [illegible] is pre[illegible] sible (Fifty% of [illegible]
(2) A type in which [illegible] can be raised b[illegible] block in [illegible] respon[illegible] [illegible] to [illegible] levels are [illegible] [illegible]ruvate be ev[illegible] by t[illegible] be [illegible] or

(3) [illegible] the [illegible]

therapy with thiamine produces no effect either clinically or on the blood pyruvate levels This would suggest not a simple thia mine deficiency but the presence of some inactivating toxin

Search for some other biochemical disturbance must be made in type 1 peripheral neuropathies Earl and Thompson (1952) have shown for example that in the peripheral neuropathy caused by poisoning with tri ortho cresyl phosphate in which pyruvate metabolism is normal there is inhibition of the activity of the enzyme pseudo cholinesterase Paralysis resulting from poisoning with some of the new organic phosphorus compounds which are used as insecticides has also been attributed to inhibition of the enzymes cholinesterase and pseudo cholinesterase (Bidstrup and his colleagues 1952a and b 1953) Cases of polyneuritis following the use of a proprietary insecticide have been described by Campbell (1952) and a case has been observed by the writer in which the same preparation was concerned These findings indicate that the differences between intoxication and nutritional deficiency as they affect intermediary metabolism within the nervous system may not be fundamental

Sinclair (1956) points out that a biochemical lesion similar to that produced by a deficiency of thiamine or pantothenic acid could also result from interference with the production or catalytic function of lipoic acid—a substance presumably formed in the liver It has long been realized that arsenical alcoholic and some forms of diabetic neuropathy resemble the neuropathy of thiamine deficiency but the actual biochemical lesion in these diseases is not known Sinclair suggests that as phosphorylation of thiamine in the liver is disturbed by alcohol and arsenic and in diabetes it is possible that lipoic acid may be concerned in some way in the aetiology of these neuropathies

Other Members of the B Complex

Pantothenic Acid Isolated deficiency of this vitamin in man is un likely to occur in view of its wide distribution in foods Like thiamine it is concerned with the oxidation of pyruvate and demyelination paralysis convulsions and coma have been induced in various species of experimental animals by deficiency of the substance There is some evidence that the burning feet syndrome in man results from panto thenic acid deficiency (Gopalan 1946) Experimentally induced defi ciency in man seems to corroborate the clinical observations (Bean and Hodges 1954)

Vitamin B_6 (Pyridoxine) Convulsions and demyelination in peri pheral nerves and posterior columns of the spinal cord have been ob tained by induced pyridoxine deficiency in animals The metabolism of glutamic acid in brain is also then disturbed (Sinclair 1956) In the

U S A *in 1952 and 1953 convulsions occurred in infants reared on a* preparation of defatted cow s milk which proved to be devoid of pyridoxine as a result probably of sterilization by excessive auto claving Cure was obtained in all cases by withdrawal of the brand of baby food (Coursin, 1954 Moloney and Parmelee 1954)

Vitamin B_{12} The unique structure ($C_{63}H_{90}O_{14}N_{14}PCo$) of this sub stance and the remarkably small requirements necessary for health suggest that it possesses some fundamental role But no enzyme con taining vitamin B_1 has yet been identified (Smith, 1956) and its role in *the functioning of the nervous system is as yet unknown Clinical* studies in pernicious anaemia in the past eight years have shown that when it is parenterally administered there is complete restoration to normal of blood and marrow and degeneration of the spinal cord is arrested Gastric atrophy and achlorhydria persist Dietary deficiency of the vitamin is rare, but Wokes Badenoch and Sinclair (1955) have encountered it in a group of persons (Vegans) who subsist on a diet devoid of products of animal origin they tend to develop peripheral neuropathy Disease of the alimentary tract is the main cause of vitamin B_{12} *deficiency normally the absorption of the vitamin depends on the* presence of intrinsic factor—a mucoprotein recently prepared in pure form from gastric juice (Latner Merrills and Raine 1954) In pernicious anaemia absorption of the vitamin as studied by radioactive techniques with estimation of hepatic uptake and excretion in faeces and urine has been shown to be grossly impaired (Witts, 1956)

Serum vitamin B_{12} estimation is a valuable diagnostic aid when spinal cord changes precede signs of megaloblastic anaemia (Gird wood 1956) Electroencephalographic studies have shown that in *pernicious anaemia with or without subacute combined* degeneration abnormal records are obtained in 60% of cases they are usually corrected by treatment with the vitamin (Samson Swisher Christian and Engel 1952, Walton Kiloh, Osselton and Farrall 1954) The degree of EEG abnormality bore no relationship to the severity of the anaemia the age of the patient or the degree of neurological involve ment

It has long been known that mental disturbance may occur in pernicious anaemia and that it is not directly related to the degree of the anaemia Recovery with vitamin B_1 is more clearly correlated with restoration of normal brain rhythms so that the vitamin may be con cerned with cerebral metabolism Cerebral respiration investigated by the nitrous oxide technique has been found to be commonly impaired in pernicious anaemia (Scheinberg 1951) Earl and his colleagues *(1953) claim to have shown that in subacute combined* degeneration of the spinal cord there is a defect of pyruvate metabolism with raised blood pyruvate levels which can be rectified by treatment with vitamin

B_1 These defects in glucose and pyruvate metabolism may be responsible for the abnormalities in the EEG

Carcinomatous Neuropathy

The aetiology of the degenerative lesions found in the central and peripheral nervous system in association with carcinoma especially of the lung is not known Subacute cerebellar degeneration sensory neuropathy motor neuropathy myopathy polyneuritis and myasthenic syndromes have been described in recent years There is no indication of any direct relationship between the tumour and the *neurological disorder and to date there is little to warrant the sugges*tion that the latter is a metabolic disturbance Some resemblance to the neuropathological findings in experimental pantothenic acid deficiency has been suggested (Denny Brown 1948 McCaughey and Millar 1955) Blood pyruvate levels are sometimes raised (Heathfield 1952 Heathfield and Williams 1954 Henson 1953 Henson Russell and Wilkinson 1954) Sinclair (1956) reports finding an abnormal concentration of *p* hydroxyphenylpyruvic acid in the blood of one case of polyneuropathy with carcinoma of the bronchus

Lathyrism

Although there is no affection of the nervous system in this country which quite resembles this disorder Lathyrism or epidemic spastic paraplegia is an important disease because of its long known association with abnormality of diet Certain peas—especially lathyrus sativus—have been substantially incriminated but the toxin responsible has not been identified

There have been many theories—vitamin deficiency of a primary or secondary nature methionine deficiency selenium intoxication or virus infection—and although there is a paucity of pathological observations it does appear as if the peculiar selectivity of the process which suddenly develops within the nervous system is a reflection of some biochemical disturbance In a study of Spanish cases the writer was struck by the predominantly male incidence the absence of cerebral symptoms suggested that it is not identical with the spastic paraplegia syndrome of prisoners of war in the Far East (Spillane 1949 *Lancet* Annotation 1953) It is possible that the elucidation of the essential disturbance in this disease may have wide implications

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SPONTANEOUS HYPOGLYCAEMIA

Spontaneous hypoglycaemia may be brought about in many ways but the great majority of cases can be grouped under three headings (Conn 1940 1947)—(1) Functional hyperinsulinism (2) Organic hyperinsulinism (3) Hepatogenic hypoglycaemia

Functional Hyperinsulinism

In this by far the commonest type of case the attacks of hypoglycaemia are usually mild in nature they are not progressive in frequency and severity and serious injury to the nervous system does not take place The distinguishing features are the occurrence of post prandial hypoglycaemia and the relief from attacks by the use of a diet high in protein and low in carbohydrate Conn found that the post prandial rise in blood sugar associated with the absorption of carbohydrate should be avoided in such cases as it produces a sharp fall in the blood sugar several hours later The slower process of glycogenesis from protein avoids undue elevation of the blood sugar and its subsequent fall Conn admits that the term functional hyperinsulinism is unsatisfactory but if it is understood that it implies an excessive functional sensitivity and responsiveness of histologically normal islet cells to the normal stimulus for insulin secretion then the term is justified until such time as a sufficiently accurate method for the determination of the concentration of insulin in the blood is devised In this type of case the patient is often a conscientious hyper reactive sensitive individual with a tendency to vasomotor instability and gastric hyper acidity Symptoms usually consist of sudden bouts of visual disturbance failure of concentration weakness trembling sweating and syncope They last for five to fifteen minutes occur two to four hours after a meal and are cut short by food They always disappear spontaneously

even though no food is taken There is transient hypoglycaemia but the fasting blood sugar is usually normal, and attacks hardly ever occur after midnight It is this type of case that may be mistakenly diagnosed as minor epilepsy, narcolepsy, neurosis or duodenal ulcer

Organic Hyperinsulinism

This is a rare cause of hypoglycaemia and is usually due to islet cell tumour or hyperplasia of the pancreas Hypopituitarism and Addison s disease may also cause hypoglycaemia it is rare in myxoedema The clinical picture in islet cell tumour may be a very striking one and many of the published case reports are very similar There were 38 cases of the syndrome due to islet cell tumour at the Mayo Clinic in twenty years (Lopez Kruger and Dockerty, 1947) In 10 314 autopsies there were 44 islet-cell tumours In this country recent reports emphasize the bizarre clinical features and the difficulties of diagnosis (Richardson and Russell 1952 Black Corbett Hosford and Turner 1954)

The attacks tend to be progressive in frequency and severity they are very liable to occur between 2 a m and 8 a m and the fasting blood sugar is always low (usually below 50 mg /100 ml) The attacks may be mild and transient or severe and prolonged In a given case the pattern of the episodes may be uniform or extremely varied There may be permanent sequelae The diagnostic triad of (1) a hypoglycaemic attack resulting from fasting or exertion (2) a blood sugar level below 50 mg /100 ml during the attack and (3) the prompt relief of an attack by glucose has been generally accepted as a reliable guide (Whipple and Frantz 1935)

The cardinal feature is the periodic occurrence in an otherwise healthy subject of episodes of disturbed consciousness or behaviour As in functional hypoglycaemia this may consist only of transient attacks with little or no impairment of awareness The release of adrenaline which converts liver glycogen into glucose has been suggested as an explanation for vegetative symptoms (sweating pallor tachycardia etc) when they are present But Richardson pointed out that his patients were flushed not pale and there is no paroxysmal hyper tension It has already (page 291) been pointed out that adrenaline can no longer be held responsible for the restoration of the normal level of circulatory glucose after insulin hypoglycaemia Its role in determining the clinical features of hypoglycaemia in man is yet to be determined although tachycardia and increase of pulse pressure can be reasonably attributed to adrenaline activity Sooner or later more serious attacks develop and they are characterized by temporary impairment of cerebral function with or without focal symptoms Transient excite ment or confusion queer behaviour with amnesia epileptic attacks periods of stupor or akinetic mutism or even prolonged coma with

decerebrate rigidity may occur There may be peculiar grimacing garrulity unmotivated laughing and crying and hallucinatory states In the phase of recovery speech may be slurred and the patient emotionally unstable Temporary focal sequelae such as aphasia or hemiparesis sometimes occur Recovery may be slow or incomplete and repeated attacks may lead to deterioration of intellect and personality Lower motor neurone lesions have been recently described (Blau Rieder and Bender 1936 Silfverskiold 1946 Lidz Miller Padget and Stedem 1949 Tom and Richardson 1951 Barris 1953) Muscular wasting with or without fibrillation has been recorded and in one case this was shown to result from destruction of anterior horn cells

During a remission fasting the patient for twelve to twenty four hours may cause a fall in the blood sugar of significant degree precipitate symptoms and induce changes in the electroencephalogram (high voltage slow activity) Difficulties in diagnosis may be encountered when the relationship of attacks to fasting is not obvious when the blood sugar has risen above 50 mg /100 ml before the patient has regained consciousness or when the response to glucose therapy is not prompt Repeated estimations of the blood sugar level may be necessary before a diagnosis can be made

Assay of serum for insulin content using the rat diaphragm method has recently proved useful in the diagnosis of islet-cell tumour of the pancreas (Willebrands and Groen 1954 Kelly 1956) The plasma insulin levels were elevated in each case removal of the tumour was followed by restoration of normal levels

Surgical removal of the islet-cell tumour is curative It appears that the surgeon may expect to find the tumour at the first exploration in 50 to 60 per cent of cases The tumour is usually small (1–2 cm) firm purplish in colour and may be embedded in the gland

Lawrence and his colleagues (1942) have shown that the neuropathological lesions of fatal hypoglycaemia due to islet-cell tumour are identical with those found in insulin overdosage in diabetics and in fatalities during the insulin treatment of schizophrenia There is widespread degeneration and destruction of nerve cells with glial proliferation the cerebral cortex the caudate nucleus and the putamen suffer most The lesions are similar in character and distribution to those found in fatal cases of epilepsy eclampsia and anoxia These authors also point out that deprivation of glucose in circulation may be complete A blood sugar of 20 mg /100 ml is common and as 20 mg in each 100 mg of reducing substances is other than glucose such a reading would mean a total absence of true sugar in the circulation Then there is failure of the normal metabolic processes in the cerebral cells During insulin therapy of schizophrenia Himwich (1951) has shown a progressive reduction of oxygen utilization by the brain and alteration

of the electroencephalograph with a falling blood sugar *Hypoglycaemia* leads to decreased cerebral metabolism and consequently impaired cerebral function, which is manifested by the appearance of clinical symptoms and alteration of the electroencephalographic pattern Anoxia produced by inhalation of nitrogen acts in a similar fashion The resistance of the newborn to hypoglycaemia and anoxia may be due to the lower metabolic activity of the infant brain

The complete cessation of brain metabolism during hypoglycaemia is prevented for a time by the formation of glucose from cerebral glycogen the release of liver glucose and by the increased oxidation of fat by non nervous tissue thus sparing the available glucose for the brain The second mechanism is the most important and depends essentially on the amount of glycogen in the liver

Hepatogenic Hypoglycaemia

Diffuse parenchymatous degeneration of the liver of infectious or toxic origin may rarely present in the form of attacks of spontaneous hypoglycaemia These may be progressive the fasting blood sugar is usually below 50 mg /100 ml, and tests of hepatic function are ab normal Occasionally the hypoglycaemia is the first indication of im paired liver function Acute necrosis cirrhosis hepatitis or chronic passive congestion of the liver may be present In liver disease generally the level of the blood sugar is usually maintained during the day so that attacks are then infrequent In organic hyperinsulinism attacks may occur by day as well as during the night

Glucose Tolerance Tests

It is the similarity between the attacks resulting from functional hyperinsulinism and those occurring in the early stage of organic hyperinsulinism which constitutes the main problem in clinical practice Fasting leads to a fall in blood sugar perhaps with the appearance of symptoms in organic hyperinsulinism but not in functional hyper insulinism The adoption of a standard three day diet before a glucose tolerance test is advocated by Conn (1947) as a helpful measure in differential diagnosis In hepatogenic hypoglycaemia there is a hyper glycaemic plateau curve with glycosuria In functional hypoglycaemia there is a sharp fall to hypoglycaemic levels between the second and fourth hours In organic hyperinsulinism the initial blood sugar is low and there is a further sharp fall to severely low levels between the second and fifth hours There is not general agreement about these statements In one of the proved islet cell tumour cases described by Black and his colleagues (1954) after a standard diet the blood sugar rose during the glucose tolerance test to a peak of 125 mg /100 ml and subnormal levels were not reached until the fourth hour

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DIABETIC NEUROPATHY

Disturbance of nerve function is very common in diabetes mellitus In pre insulin days the incidence of neuropathy was generally reported as between 30 and 50 per cent Recent reports mention figures of 48 per cent (Broch and Klovstad 1947) 93 per cent (Collens Rabiner Zilinsky Boas and Greenwald 1950) 57 per cent (Hirson Feinmann and Wade 1953) 17 per cent (Martin 1953b) and 62 per cent (Goodman Baumel Frankel Marcus and Wassermann 1953) Incidence of the more severe manifestations has declined with modern diabetic control but there is still much which is obscure concerning the types of neurological complication and their pathology and relationship with the metabolic disturbance

The main symptom of diabetic neuropathy is pain This is most often felt in the lower limbs and may be severe and most troublesome at night or in cold weather It may be burning or aching in character, ill defined or well localized, and sharp attacks of pain may be accompanied by tenderness and hyperalgesia Weakness some muscular wasting impairment of sensation and loss of ankle reflexes are likely to develop in many cases The signs are often asymmetrical and may be accompanied by trophic changes in the feet slight ataxia (diabetic pseudo tabes) with considerable loss of vibration sense and some degree of dissociated sensory impairment Impairment of vibration sense in the lower limbs is particularly common in diabetics without neuropathic symptoms Signs are uncommon in the upper limbs and it is doubtful whether oculomotor and facial palsies are an essential part of the clinical picture Impairment of the pupillary light reflex may be observed The cerebrospinal fluid protein content may be raised Garland and Taverner (1953) have recently reported five cases of diabetic myelopathy characterized by the onset of pain in the legs loss of reflexes weakness wasting and normal superficial and deep sensibility three patients had extensor plantar reflexes Four had raised protein in the spinal fluid The patients were middle aged with untreated diabetic symptoms of relatively short duration and four out of the five responded well to treatment of the diabetes

There is a second group of symptoms which should be mentioned in diabetic neuropathy They relate to disturbance of autonomic function of peripheral nerves Perforating ulcers with absence of sweating of the feet atrophy of the skin changes in the toe nails and impairment of reflex vasoconstriction and vasodilatation in the lower limbs in response to cooling and heating the trunk have been described (Lister and Maudsley 1951 Martin 1952 and 1953a) Neuropathic arthropathy is also being increasingly recognized in patients with diabetic neuropathy Painless destructive lesions of the tarsal joints occur similar to those found in tabes dorsalis and syringomyelia The precise aetiology of the neuropathic arthropathy is not known ischaemia autonomic disturbance and repeated minor traumata to insensitive tarsal joints have all been implicated

Nocturnal diarrhoea nocturnal faecal incontinence neuropathic bladder and impotence have also been attributed to autonomic disturbance (Rundles 1945 Treusch 1945 and others) Diabetics without neuropathy may also show evidence of disturbed autonomic innervation

Probably the characteristic clinical features of diabetic neuropathy consist of the predominance of sensory symptoms the loss of the ankle reflexes and the occurrence of autonomic disturbances These neuropathic disturbances may not be the only complications of diabetes

Retinopathy nephropathy and cardiovascular degeneration are commonly present Thirty three per cent of Martin s 150 cases of diabetic neuropathy showed diabetic retinal disease There were only two cases of diabetic renal disease He was able to show however that diabetic retinopathy is related mainly to the duration of the metabolic disorder it is not commoner in diabetic neuropathy than in the general diabetic population Delay in diagnosis is most likely to occur when the neuritic pain is acute in character and onset or when it is localized to an intercostal or lumbar position or when it is in the proximal part of a limb

There have been three main theories concerning the aetiology of diabetic neuropathy (1) degenerative vascular disease (2) vitamin deficiency (3) the disordered metabolism of diabetes mellitus

Degenerative vascular disease is common in diabetes and almost invariable in adult diabetics so that its presence in cases of diabetic neuropathy is to be anticipated Woltman and Wilder s (1929) findings are often quoted They found constant arteriosclerosis of the nutrient vessels of the nerves in all their ten cases but this is not surprising in view of the age of the patients and the fact that in six of them examination of the nerves was made in a limb amputated for arteriosclerotic gangrene Of Rundle s (1945) cases of diabetic neuropathy only 25 of 125 had clinical evidence of peripheral vascular disease Only 10% of Broch and Klovstad s (1947) neuritic cases and 33% of Martin s 150 cases were similarly affected Goodman and his colleagues (1953b) found that despite the high incidence (46%) of occlusive peripheral vascular disease in diabetics the development of neuropathy cannot be correlated Experience indicates rather that the presence of diabetes in cases of peripheral vascular disease increases the incidence of neuropathy Martin (1953b) found that skin temperature studies and oscillometric readings did not suggest that vascular disease was important in the aetiology of diabetic neuropathy The latter can occur with a good peripheral circulation and is frequently absent in cases with severe ischaemia

Deficiency of vitamin B_1 was inevitably incriminated as in other forms of peripheral neuropathy but few would now maintain that absolute or relative deficiency of this substance or its usefulness in treatment have been demonstrated in diabetic neuropathy A malnourished diabetic with neuropathy may lack vitamin B_1 but the majority of case reports purporting to show that the neuropathy responds to treatment with this vitamin are not convincing The slowness of the response and the lack of consideration given to simultaneous control of the diabetic state make the claims invalid Pyruvic acid metabolism so typically affected in B_1 deficiency is not impaired in this form of peripheral neuropathy Recently vitamin B_{12} has been claimed to give specific relief in diabetic neuropathy (Duncan 1952)

but the writer s experience has been to the contrary (I have twice seen failure to relieve pains and paraesthesiae with vitamin B_{12} disclose a mistaken diagnosis of subacute combined degeneration, both patients were suffering from diabetic neuropathy)

The difficulties in relating the neuropathy directly to disordered metabolism may be summarized as follows *First* the neuropathy may develop before recognizable diabetes, but this of course does not mean that fundamental metabolic changes are not already present *Second* there is no close correlation between the occurrence of the neuropathy and the severity of the diabetes *Third* the neuropathy may appear shortly after the commencement of treatment with insulin *Fourth* accurate control of the diabetes yields varying results as far as the neuropathy is concerned Nevertheless neuropathy seems to be related in some way to the diabetic disorder itself In Rundle s series (1945) of 125 cases of neuropathy 75% had lost over twenty five pounds in weight In Martin s 150 cases of diabetic neuropathy 58 had had no treatment 90 had lost much weight 19 had hepatomegaly, and only 80 were taking insulin at the time of onset of the neuropathy The neuropathy cannot be correlated with glycosuria or acidosis or any particular complication of diabetes but it is commonly suggested that lack of diabetic control is responsible In the writer s experience how ever this explanation is not satisfactory Neuropathy seems to be evenly distributed among the adult diabetic population irrespective of the duration or severity of the diabetes the neuropathy may be just as serious in the controlled as in the uncontrolled diabetic When the neuropathy develops after the introduction of insulin it can also be very disabling For these reasons the belief that neuropathy is a result of long continued poor control of the diabetes appears to be un justified

The pathology of diabetic neuropathy requires much more study There is degeneration of the peripheral nerves and posterior spinal roots but changes in the anterior horn cells and in the posterior and lateral columns of the spinal cord have also been described (Garland and Taverner 1953) Martin (1953b) has studied biopsy specimens of affected nerves from ten cases of diabetic neuropathy and found conspicuous degeneration of axis cylinders and myelin sheaths without signs of inflammatory reaction in all cases Small calibre non myelinated fibres suffer most and thus may explain the frequency of burning paraesthesiae and autonomic disturbances In ischaemic neuropathy on the other hand the larger myelinated fibres are first affected and impairment of tactile sensibility precedes that of pain

Mirsky (1953) concludes from a study of the premature development of arteriosclerosis and impairment of vibratory sensibility which occurs in diabetes that they are concomitants rather than complica

tions of the metabolic disturbance The syndrome of diabetes mellitus in man is due to two independent components one of which results in insulin insufficiency and the other in an accelerated rate of neuro vascular damage

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THE LIPIDOSES

Until recently the lipids (or lipoids) were defined as chemical com pounds which are insoluble in water and soluble in so called fat sol vents (e g ether and chloroform) The term included not only the true fats (triglycerides) but other substances which are related to fats by virtue of common physical or chemical properties Classification of the lipids is now being based increasingly on chemical constitution

Those of clinical interest are

(1) The phosphatides (lecithins cephalins and sphingomyelins)
(2) The cerebrosides (e g kerasin)
(3) The gangliosides
(4) The sterols (e g cholesterol)

Klenk (1953) outlines the relationship between sphingolipids (lipids containing the base sphingosine) as follows

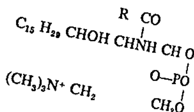
Sphingolipids

(1) *Sphingomyelins*

Fatty Acid

Sphingosine

Choline

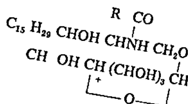


(2) *Cerebrosides*

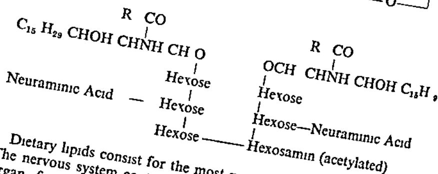
Fatty Acid

Sphingosine

Hexose



(3) *Gangliosides*



Dietary lipids consist for the most part of glycerides of fatty acids. The nervous system contains larger amounts of lipid than any other organ; fatty substances comprise over one half of the solid matter in brain and are mainly found in myelinated structures. The specialized nature of the myelin sheath with its uniquely high ratio of lipid to protein is a biochemical peculiarity shared perhaps only with the enveloping membrane of the erythrocyte (Lumsden, 1951).

The thin semi-insulating membrane that encloses all neurones and axones also possesses lipid properties. As this membrane is intimately concerned with the spread of activity and the diffusion of electrolytes it clearly plays an important role in the preservation of the stability of the nerve cells. Within the neurones themselves, in the mitochondria and nuclei, lipid substances are also found.

In the lipid storage diseases or lipidoses there is an accumulation of one or more lipid substances in the cells of the reticulo-endothelial system, spleen, lymph nodes, bone marrow and various viscera. The

ganglion cells of the nervous system may be affected either with or without involvement of the reticulo endothelial system The term *neuronal lipidosis* has been proposed (Bird 1948) for the group of cases with involvement of the nervous system using a classification based on the type of lipid concerned

(1) **Cerebroside Neuronal Lipidosis** Associated cerebroside infiltra tion of reticulo endothelial cells—*Gaucher s disease*
(2) **Phosphatide Neuronal Lipidosis**
   (*a*) Without involvement of the reticulo-endothial system (*Amaurotic family idiocy or cerebro macular degeneration*)
   (*b*) With involvement of the reticulo endothelial system (*Niemann Pick disease*)

The xanthomatoses involve the nervous system mainly as a result of the accumulation of lipid material in the reticulo-endothelial system but foci of demyelination glial reaction and foam cells have been described Cholesterol is the only lipid present in the blood serum in health or in the various lipidoses In the brain it exists almost entirely in the free form whereas in other organs it is to be found mainly in the form of esters Cholesterol is synthesized in the brain especially during the first year of life when the process of myelination is very active Serum cholesterol is increased in only one type of xanthomatosis

The mechanism causing this group of diseases is thought to be an intracellular disturbance of lipid metabolism There is no accumulation of intermediate metabolites in the blood stream as in disorders of inter mediary metabolism There are infantile and adult forms of these syndromes and a familial and racial (Jewish) tendency is present in some of them The processes of accumulation of the lipid in the nerve cells with the eventual rupture and disintegration of the cell may be subacute or chronic Blindness spastic paralysis extrapyramidal and bulbar syndromes with progressive dementia are the main neuro logical features of the syndromes Progressive myoclonus epilepsy may also be a manifestation of neuronal lipidosis (Watson and Denny Brown 1953)

In Gaucher s disease and Niemann Pick disease the lipid substances which accumulate in the viscera have been identified as cerebrosides and sphingomyelins respectively In the infantile form (Tay Sachs) of cerebromacular degeneration recent studies indicate that gangliosides accumulate in the nerve cells (Klenk 1953) This author points out that cerebrosides sphingomyelins and gangliosides which are all normally present in small amounts in healthy nervous tissue contain sphingosine as a characteristic component Cerebrosides and sphingomyelins are found mainly in the white matter of the brain and are probably con stituents of the myelin sheaths Gangliosides about which less is known

are found mainly in grey matter and may be normally present in the nerve cells Diseases resulting from the abnormal storage of the phosphatides cephalin and lecithin have not been described

THE NATURE AND DISTRIBUTION OF THE ACCUMULATING LIPID IN NEURONAL LIPIDOSIS

	Gaucher s Disease	Niemann Pick s Disease	Tay Sachs Disease
Viscera	Glucocerebrosides	Sphingomyelins	?
Brain	?	Gangliosides	Gangliosides

In Gaucher s disease which is usually familial and shows a predilection for female members of the Jewish race the stored lipid is the cerebroside kerasin In normal brain and viscera this exists mainly as galactocerebrosides glucocerebrosides are not usually present In Gaucher s disease however glucocerebrosides accumulate in the viscera but are not found in the brain itself Although Gaucher s disease is the commonest form of lipidosis involvement of the nervous system is actually rare and the disorder in the ganglion cells of the brain is not due to the accumulation of cerebrosides (Thannhauser 1953) Its nature is not known

The patient is usually an infant or child and abdominal enlargement attracts attention This proves to be due to enlargement of spleen and liver The skin may show a copper coloured pigmentation and brownish plaques on the conjunctiva and cornea (pingueculae) are said to be pathognomonic There may be anaemia and thrombocytopenia with haemorrhagic tendencies Involvement of the nervous system is indicated by mental deterioration apathy stupor catatonic attitudes and mascular hypertonicity with increased reflexes Death usually ensues within a year of the onset of cerebral involvement Otherwise the disease is noted for its chronicity

In Niemann Pick disease the accumulating lipid in the viscera is the phosphatide sphingomyelin but in the ganglion cells of the brain sphingomyelin does not accumulate Gangliosides are the lipids which balloon the neuronal cells (Klenk 1953)

In this disease which is confined to infancy and early childhood the Jewish race is again particularly liable but the familial tendency is not striking The liver and spleen rapidly enlarge lymphatic glands are swollen and there is usually anaemia and brownish cutaneous pigmentation The disease may not be a clinical entity in view of the established relationship with amaurotic family idiocy (Bird 1948) The two diseases may be found in one family and histological studies have shown that the neuropathological findings are identical Nevertheless there is no accumulation of sphingomyelin in amaurotic family idiocy

Cerebromacular Degeneration (Amaurotic Family Idiocy) Degenera

tion of the ganglion cells of the retina and brain resulting in blindness and progressive cerebral disorder constitute the main features of this disease It is familial and in some of its forms it has a marked pre dilection for Jews There are two main types—the infantile (Tay Sachs) and the juvenile (Batten Mayou)—which differ mainly in re spect of the age of onset and the rate of progress Congenital and adult forms of the disease have also been described

THE INFANTILE TYPE which occurs most frequently in Jewish females usually develops at about the age of six months and is fatal in a year or so Mental retrogression is associated with progressive paralysis spasticity and blindness The cherry red spot in the fundi is character istic and is due to the appearance of the vascular choroid in the macular region consequent on degeneration of the ganglion cells of the retina The lipid concerned is mainly ganglioside

THE JUVENILE TYPE generally has its onset about the sixth year and runs a fatal course of several years Visual failure may precede mental deterioration and paralysis and make early diagnosis difficult There is no cherry red spot but degeneration of the outer granular layer of the retina occurs and the macular area becomes mottled

The fundamental histological changes in these neuronal lipidoses are identical Symptoms seem to depend on the area of the brain most affected *In certain age groups this may be related to the process of* myelination widespread arrest of myelination has been described in early cases The lipid content of the white matter of the infant brain unlike the adult brain differs little from that of the grey matter On the other hand the onset of these disorders in adult life may be related to the fact revealed by isotope studies that brain lipids are not stored in a static manner but are in a state of constant metabolic turnover or dynamic equilibrium The various neuronal lipidoses may then be regarded as manifestations of alternative modes of breakdown of the intracellular chemistry of the neurone (Brain 1953)

Little is known of the chemistry of myelination and demyelination and although demyelination may be only the visible sign of one of a number of different processes (copper deficiency vitamin B deficiencies intoxication by cyanides or anticholinesterases) within the sheath the lipids clearly have important structural functions It is thought that cholesterol cerebroside and phosphosphingoside are the three main lipids of the myelin sheath (Rossiter 1955) There is also evidence that the sheath consists of an alternation in concentric layers of lipids and proteins In disseminated sclerosis Cumings (1953) has found loss of phosphatides in the demyelinated areas which may contain cholesterol esters Demyelination can of course result from many different noxious agents but there appear to be only two varieties of true primary demyelinating disease in man

(1) The leucodystrophies or leuco encephalopathies (heredo degenerative)
(2) Disseminated sclerosis and Schilder s disease (Lumsden 1951)

In the leuco encephalopathies the presence of 'prelipid substances and products staining metachromatically with basic aniline dyes are a characteristic feature Metachromasia especially affects the oligodendroglia a cell long suspected of having something to do with the nutrition of myelin It has been postulated that the metachromatic substances are or are related to sphingosides or cerebrosides A possible relationship with the general lipidoses comes from the observation that in these leuco encephalopathies the metachromatic substances are not limited to the central nervous system but have been found also in other tissues—kidney liver gall bladder pituitary and testis

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KERNICTERUS

The term kernicterus was coined by Schmorl in 1904 to describe yellow pigmentation of the basal ganglia of infants dying from neonatal jaundice The pigment is found not only in nerve cells but in phagocytes and in the interstitial tissue While it is found most constantly in the nuclear masses—the putamen the subthalamic nuclei the hippocampus the dentate nuclei and the inferior olives—it is not confined to them cortical and subcortical lesions may be present The ganglion cells of

the pigmented areas are severely injured There has been much speculation concerning the nature of the pigmentation which is now thought to be bilirubin (Dereymaeker 1949 Claireaux Cole and Lathe 1953)

Several siblings may be affected Prematurity is common but the baby is usually normal at birth Jaundice develops in the first few days and is quickly followed by the appearance of nervous symptoms There is fluctuating muscular rigidity opisthotonos and muscular twitchings Convulsions may occur If the infant survives the acute illness there is a latent period of a few weeks or months during which the baby may appear to be normal But muscular hypotonia develops and is soon followed by the onset of involuntary movements which become choreic or athetoid in due course There is retarded development and emotional instability Survivors from acute kernicterus in the first week of life seem never to be normal at the end of the first or second year Eighty per cent of the older patients show choreoathetotic types of disturbance and many are mentally deficient 30–80% have an appreciable perceptive type of deafness 50–60% die in early life (Evans and Polani 1950 Gerrard 1952) Motor and sensory disabilities may mask intelligence in some cases

The demonstration of rhesus incompatibility in icterus gravis neonatorum and in kernicterus (de Bruyne and van Creveld 1948) suggested an explanation for the disorder But it was not long before it became clear that kernicterus occurred in premature infants without any pathological or serological evidence of haemolytic disease (Aidin Corner and Tovey 1950 Govan and Scott 1953) The latter authors examined the brains of three non jaundiced premature infants who had lived only 48 to 72 hours following difficult births They found histological evidence of brain damage indistinguishable from that seen in kernicterus due to haemolytic disease They concluded that anoxia is the main factor and pigmentation a secondary feature Nevertheless erythroblastotic infants born at full term are not invariably anoxic Until jaundice appears all seems to be well signs of nervous disorder never precede jaundice

Infants who survive and develop neurological disability have similar but less marked pathological changes in the brain Crome (1955) reports widespread loss of nerve cells in the cerebral cortex and a more localized change in the globus pallidus and more rarely in the corpus Luysii Such changes are not of course specific for Rh sensitization Meriwether Hager and Scholz (1955) considered that the nature and pattern of the lesions in survivors suggested that hypoxia was the main factor they found symmetrical and total loss of cells in the globus pallidus

A recent survey of the incidence of kernicterus showed that about one quarter of the cases are associated with prematurity and are clearly

distinguishable from the remainder which are associated with haemolytic disease (Claireaux *et al* 1953) But despite the different pathogenesis these authors found the same distribution of the pigment in the brain in the two types of case and from a study of the diazo reaction the chromatographic behaviour and the absorption spectrum they concluded that the pigment was bilirubin in each instance Brain tissue appears to contain a lipid which has a selective affinity for bilirubin This may explain why in the obstructive jaundice of adults or in that due to atresia of the bile ducts in the newborn brain jaundice does not occur In these disorders it is not bilirubin but the 'direct reacting bile pigment which is the main pigment to which the brain is exposed (For a fuller consideration of bile pigments see Chapter 5)

Kernicterus has been described in familial non haemolytic jaundice (Crigler and Najjar 1952) and experimentally, bilirubin can cause a brain lesion similar to that of kernicterus (Kuster and Krings 1950) Gerrard (1952) found that hypoglycaemia was inconstant anoxia unlikely, and considers that pigmentation of the brain and damage to the liver resulted from some primary biochemical disorder The reason for the location of the lesions and the relationship between the nerve cell and pigmentary abnormalities remain unknown

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MYASTHENIA GRAVIS

The abnormal fatigability or variable paralysis of voluntary muscle in myasthenia is due to a disturbance in the peripheral neuromuscular apparatus most probably at the myoneural junction and constitutes the principal symptom of the disease This weakness after voluntary contraction differs in some respects from physiological fatigue on which neostigmine has no effect In myasthenia the affected muscles do not ache and are not tender The intensity of the weakness which develops on exercise in myasthenia is not simply a reflection of the state of the muscles prior to their use as in normal fatigue Moreover myasthenic paresis may be restricted to one group of muscles and existing weakness may be aggravated by exercise of a remote group of muscles For example in a patient of mine a masseuse ptosis was increased by vigorous exercise of the arms Normal fatigue and myasthenic fatigue also differ electromyographically Although for many years it has been considered a phenomenon of the nervous system physiological fatigue is almost certainly peripheral in origin and due to failure of the muscles to contract when motor impulses reach them (Merton 1956) Physiological fatigue is not however due to blockage of impulses at the neuromuscular junction as in myasthenia For these reasons it is obvious that the fatigability of myasthenic muscles is not as perhaps its name implies anything akin to normal muscular fatigue

The explanation of the peculiar localization of the pareses which characterize many cases of this disorder is not known Muscles concerned in ocular and facial movement and in mastication swallowing and speech are particularly vulnerable and in an affected limb some muscles may be more involved than others When the weakness is generalized it remains confined to the voluntary musculature cardiac and smooth muscles are not affected The disease is probably commoner in the female but is usually little influenced by menstruation pregnancy and the act of labour It usually appears in the third decade but may be seen in old people children and even in newborn infants (twelve cases of neonatal myasthenia have been reported) Neonatal myasthenia is usually transient and as the great majority of myasthenic mothers give birth to normal children and none of the reported cases of neonatal myasthenia have developed myasthenia in later life it seems probable that these infants are not essentially myasthenic but eceive from their mothers via a defective placenta some curare like ibstance which is subsequently destroyed (Gans and Forsdick 1953)

Myasthenia commonly behaves in an unpredictable manner the course is usually long and fluctuating and remissions are not commonly complete The weakness may remain confined to one group of muscles for many years (e g ocular muscles) but progressive deterioration with spreading of the weakness may occur It is thus unpredictability that

makes assessment of the value of thymectomy so difficult The introduction of this operation incidentally revealed the existing lack of information of the natural history of the disease—a not unfamiliar consequence of new therapy When there is a thymic tumour the course of myasthenia is more rapid and progressive

The affected muscles do not usually waste and reflexes and sensation remain intact Fibrillation is rare The so called myasthenic reaction is of little diagnostic aid, it is not constant and may be found in other diseases The affected muscles retain the ability to respond to the galvanic current but stimulation with a faradic current leads to an initial response with a rapid falling off of the degree of contraction

The effector mechanism comprising a single motor nerve fibre with its branches terminating in 100–200 muscle fibres is termed the motor unit Electromyography is concerned with the recording of the electrical activity of this unit In complete relaxation there are no action potentials from normal muscle but Brazier (1944) has reported that myasthenic muscle exhibits some diffuse electrical activity Voluntary contraction of normal muscle is associated with rhythmic electrical discharges of a certain amplitude fatigue causes a reduction in the number of spikes but not of their amplitude In myasthenia the amplitude of the spike varies during the actual contraction of the muscle and fatigue causes a progressive diminution in their amplitude (Lindsley 1935 Harvey and Masland 1941 Brazier 1944) A variation in the number of contracting muscle fibres of a motor unit in response to an impulse from the anterior horn cell may be responsible for these phenomena There is also evidence that the refractory phase of the excitatory process is prolonged in myasthenia (Pritchard, 1933) Johns Grob and Harvey (1955) investigated the electromyographic changes in generalized myasthenia and found that there is a slight degree of block to the passage of a single impulse following which there is a transient (10 sec) increase in the degree of block The degree of block waxed and waned with continued stimulation and these authors considered that the EMG characteristics of myasthenic block closely resembled those produced by d tubocurarine in normal subjects

Myasthenia is sometimes found in association with hyperthyroidism but the effects of treatment of the hyperthyroidism on the myasthenia are inconstant Other endocrine abnormalities have been described in association with the disease but cortisone and ACTH do not appear to have any consistent influence in myasthenia It has always been taught that the only constant morbid anatomical changes in the disease consist of lymphorrhages (small collections of lymphocytic cells) in muscles and certain viscera and abnormalities in the thymus gland Recently however Russell (1953) reported three types of histological change in myasthenic muscles

(1) Acute necrosis with inflammatory cellular reaction
(2) Progressive atrophy of muscle fibres with lymphorrhages and
(3) Simple atrophy of a different character from that of the second type

Although these changes are not peculiar to myasthenia gravis they must be responsible for certain clinical features and may be the basis for the condition of Myasthenic Myopathy described by Walton and Nattrass (1954) In 10 to 15% there is a thymic tumour in 75% there is lymphoid hyperplasia with the formation of germinal follicles in the medulla of the gland Involutional changes in the thymus are found in 15% of cases Extracts from thymus glands of myasthenic patients removed at operation appear to possess the property of depressing the muscle response to nerve stimulation (Wilson Obrist and Wilson 1953) Glands which on removal produced the most beneficial therapeutic effect also showed the most activity in this respect Control observations suggested that normal adult thymic extract is relatively inactive although that from children is active The degree of activity of the Myasthenic Thymus in these experiments bore no direct relationship to the severity of the myasthenia Wilson and Wilson (1955) point out that the effect on the nerve muscle preparation is not to produce all the characteristic features of myasthenia gravis and it cannot be reversed by neostigmine

Neuromuscular Transmission in Myasthenia

The exact nature of the neuromuscular block in myasthenia is still not known but there is good evidence that it consists of an alteration in the response of the motor end plate to acetylcholine Normally the electrically conducted nerve impulse reaching the end of a nerve fibre releases acetylcholine—a substance which has no known excitatory effect on nerve fibres themselves (Dale 1948) At the myoneural junction there is a resulting depolarization of the muscle surface membrane and contraction of muscle fibres While it is depolarized the end plate cannot be stimulated (depolarization block) The interchange of sodium and potassium ions which provided the energy for the propagation of the nerve impulse also provides for its propagation along the muscle fibre The liberated acetylcholine is rapidly hydrolysed into acetate and choline by the enzyme cholinesterase which is present in muscle tissue and in greatest concentration in the vicinity of the motor end plates

This chemical transmission of the excitatory process from the endings of the motor nerve fibres to the motor end plates could be disturbed in several different ways but with superficially similar effects (Dale 1948) Thus there might be

(1) Failure of conduction in the terminal branches of the nerve fibre
(2) Failure of adequate liberation of acetylcholine This could result either from lack of this substance at the nerve endings or because the arrival of the nerve impulse does not cause it to be yielded up
(3) Excessive cholinesterase activity
(4) Persistent depolarization due to (*a*) deficient cholinesterase or (*b*) cholinesterase inactivators or (*c*) non hydrolysable analogues of acetylcholine
(5) Lack of response to acetylcholine

Experiment has shown that neuromuscular transmission can in fact be interrupted by different toxins in various ways Thus *curare* blocks transmission not by stopping conduction in the nerve terminals but by rendering the end plates insensitive to acetylcholine the end plate remains normally responsive to electrical stimulation (competitive block) On the other hand the toxin of *Bacillus botulinus* prevents the liberation of acetylcholine The *tetanus toxin* affects neuromuscular transmission in yet another way The nerve terminals fail to maintain an adequate store of acetylcholine so that when the nerve impulse arrives only a weak muscle twitch results There is a continuous leak of acetylcholine on to the motor end plates with resulting muscle spasm *Decamethonium* and *choline* produce depolarization block and this is intensified by acetylcholine or neostigmine The investigation of neuro muscular blocking agents in the past decade has been confusing to follow but results point to the following classification

(1) *Depolarizing Blocking Agents* Decamethonium Choline Neo stigmine and Edrophonium (Tensilon),
(2) *Non Depolarizing Blocking Agents* Tubocurarine Flaxedil Mytolon

In myasthenia gravis there is no evidence of deficiency of acetyl choline nor of excess of cholinesterase (Wilson Maw and Geoghegan 1951) and the myoneural junction remains sensitive to acetylcholine (Wilson and Stoner 1947) Interference with the normal action of acetylcholine by a toxin with a curare like effect remains a possibility In spite of the difference between the defect of neuromuscular trans mission in myasthenia and in a curare paralysis substances which reduce myasthenic weakness such as neostigmine ephedrine am phetamine potassium and guanidine all possess an anti-curare effect in the experimental animal Curare and drugs with curare like effect, such as quinine aggravate myasthenia Although neostigmine is an anticholinesterase its effect in myasthenia gravis may also be due to the fact that it acts as a direct antagonist to a curare like blocking substance It has been claimed in fact that the serum of patients with

myasthenia contains a substance which produces a block in neuro muscular transmission in the isolated nerve muscle preparation of the frog (Wilson and Stoner 1944) Neostigmine retains its excitatory effect on muscle when cholinesterase has already been inactivated by another anticholinesterase (diisopropylfluorophosphonate DFP) Its efficiency in myasthenia may depend on this dual activity (Riker and Westcoe 1946) Since the introduction of alkyl phosphate agents with strong anticholinesterase activity in the treatment of myasthenia it has been observed that small doses of neostigmine enhance their effect (Osserman and Kaplan 1953)

More recent investigations (Grob Johns and Harvey 1955) of the effect of intra arterial injections of acetylcholine upon muscle action potentials in normal and myasthenic individuals indicate that the choline formed by breakdown of acetylcholine plays a hitherto un suspected part in muscle contraction In the normal subject choline behaves as does acetylcholine but in the myasthenic patient it has a curare like effect In the normal subject choline produces a depolarizing block whereas in the myasthenic patient it establishes a competitive block namely one which is abolished by raising the concentration of acetylcholine These workers conclude therefore that the block in neuromuscular transmission in myasthenia gravis is produced by choline released in a normal manner Churchill Davidson and Rich ardson (1953 and 1955) had already found that in normal subjects decamethonium block is due to simple depolarization but that in myasthenia it is of the dual type—transient depolarization is followed by a more prolonged non depolarization (i e curare like block) Both of these investigations support the view that the essential ab normality in myasthenia gravis lies in an alteration in the response of the motor end plates and not in the presence of a curare like substance in the circulation

Diagnosis and Treatment

In the majority of cases the reponse to a subcutaneous (1 5 mg) or intra arterial (⅜ mg) injection of neostigmine provides a satisfactory diagnostic procedure In myasthenia confined to the ocular muscles the effect may be difficult to judge and photographs before and after the test dose may be helpful When myasthenic muscles cease to respond to neostigmine withdrawal of the drug for a week or two is often followed by a further period of response Osserman and Teng (1956) have used a new short acting cholinergic drug *Tensilon* (edrophonium chloride) in diagnostic tests and report positive responses in 93% of myasthenics Intravenous injection (2 to 8 mg) increases muscle strength within 30 to 40 seconds the effect lasts five minutes In the normal subject it merely produces fasciculation

The search for drugs with longer action and less side effects than neostigmine continues Osserman (1955) reports on the use of *Mestinon* (pyridostigmine) a pyridine analogue of neostigmine The drug acts with less side effects but not for much longer during the diurnal hours than neostigmine Its effect during the nocturnal hours is more pro longed and relief of weakness of ocular and bulbar muscles is better than with neostigmine Tether (1955 and 1956) has had similar experiences with this drug so that it may prove helpful when resistance to neostig mine is present when unpleasant side effects are troublesome or when neostigmine does not prevent paralysis on waking

Schwab (1955) reports on a trial of another new substance *Mysuran* whose structural formula can be compared with neostigmine It too has a longer action than neostigmine and is less likely to produce gastro intestinal disturbances when the therapeutic dosage is reached

Myasthenic and Cholinergic Crises

There are two types of crises (failure of muscles concerned with respiration and/or swallowing) which may be met with in myasthenia gravis The true myasthenic crisis is due to insufficient medication or drug resistance and is widely known The cholinergic crisis has only recently been recognized Grob Garlick Merrill and Freimuth (1949) first reported cholinergic crises in healthy individuals exposed to anti cholinesterase insecticides They classified the symptoms as muscarinic nicotinic and central nervous system in type Wilson Williams and Miller (1952) described the occurrence of such crises in myasthenic patients overtreated with cholinergic drugs The two types of crisis may be very similar but, apart from acute restlessness and panic the paralysis of the myasthenic crisis is not accompanied by the other distressing features of cholinergic poisoning (viz salivation pallor, sweating gastro intestinal stimulation fasciculation etc) The danger of cholinergic crises is considerable when regular treatment with bella donna may obscure the early gastro intestinal symptoms of the impend ing crisis When signs of a cholinergic crisis appear the responsible drug should be stopped and the emergency measures necessary for the management of bulbar and respiratory paralyses must be undertaken Intravenous atropine may be necessary

Thymectomy

The value of thymectomy in this disease remains debatable Few clinicians would advise it in ocular myasthenia where the weakness may remain localized for many years In generalized myasthenia the natural prognosis is not good Thymectomy is contra indicated when there is a thymoma (15% of cases) Keynes (1954) states that in some 200 cases of thymectomy (without thymoma) the operative mortality of

42% with remission of the disease in 65% which he reported in 1949 were figures which remained much the same Eaton and Clagett (1955) consider thymectomy of value when there is no thymoma and the patient is a female under the age of 50 Satisfactory remission took place in 50% of an operated group in 20 to 25% in the unoperated Schwab Viets Vanderveen Cope Sweet and Castleman (1955) concluded that in females under 35 thymectomy produced remissions in 65% within a year (in controls 17%)

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PERIODIC PARALYSIS

The part played by the potassium ion in normal and pathologica physiology is dealt with in Chapter 2 In the condition or group o conditions known as periodic paralysis which may be familial o sporadic, there is recurrent flaccid paralysis affecting the limbs an trunk muscles with loss of deep reflexes and of electrical excitability o muscles Sensation remains normal and consciousness is unimpaired The muscular weakness may be slight or severe in degree and extent In severe attacks the facial bulbar and respiratory muscles may b affected An attack usually lasts several hours and it may develop spontaneously or after excitement a heavy meal during sleep and i can sometimes be induced by the local application of cold or by th administration of adrenaline glucose or insulin Affected individual are usually otherwise healthy but persistent slight muscular weakness has occasionally been observed and rarely there is eventual muscular atrophy Smooth muscle is not affected and electrocardiographic changes are milder than those seen in hypo and hyperkalaemia arising in other illnesses Males are affected more often than females and the disorder usually first manifests itself in the second decade attacks tend to diminish in severity and frequency with increasing age The pattern of inheritance is variable in the familial cases there is a great diversity and variety of expression of the inherited abnormality

The metabolic nature of the familial disorder was shown by Biemond

and Daniels in 1934 and by Aitken Allott Castleden and Walker in 1937 when they demonstrated that the serum potassium fell to low levels during an attack and that muscular power could be restored by the administration of potassium chloride by mouth There may also be a significant fall in serum phosphate Neither of these substances is lost in the urine but migrates to some site in the tissues possibly the liver and muscles The fall in serum potassium itself is not responsible for the paralysis in a given case it may occur spontaneously or be induced artificially without subsequent paralysis In normal people also similar falls in serum potassium without the development of paralysis may be induced by repeated injections of adrenaline Allott and McArdle (1938) came to the conclusion that the low serum potassium was only one factor in producing an attack an abnormality in the neuromuscular apparatus being another essential part

In hypokalaemic states resulting from renal or gastro intestinal loss severe depletion of potassium is necessary before paralysis ensues In familial periodic paralysis hypokalaemia is rarely as severe the thres hold level is usually 3-3 5 m equiv /L Most authors report no correla tion between the depth of the paralysis and the level of the serum potassium Indeed paralysis may occur without hypokalaemia (Watson 1946 Tyler Stephens Gunn and Perkoff 1951) In sporadic periodic paralysis the serum potassium is occasionally increased (Bull Carter and Lowe 1953) Lastly McArdle (1956) mentions a family with periodic paralysis in which he has observed a slightly raised serum potassium during the attacks there was a tendency to increased excre tion of potassium during the paralysis These observations suggest that there may be more than one type of sporadic and familial periodic paralysis but most observations have been made on the classical familial variety in which a fall in serum potassium takes place

In this classical group there is a marked positive balance of potas sium the fall in serum potassium concentration is accompanied by a fall in urinary excretion of potassium The cause of the transfer of potassium into the cells is not known Zierler and Andres (1956) have shown that there is a nocturnal shift of potassium into muscle cells which is much greater in patients with periodic paralysis than in healthy people This may explain the tendency for attacks of periodic paralysis to start in the early hours Despite the association with some disorder of carbohydrate metabolism which experiments with adrena lin glucose and insulin suggested no actual proof of such a biochemical lesion has come to light Conn and his colleagues (1956 and 1957) have further shown that the relationship between serum potassium and muscular paralysis is complex They found that attacks of paralysis were preceded by massive retention of sodium and increased urinary excretion of aldosterone Sodium diuresis accompanies recovery

When their two patients were put on a low sodium diet it was no longer possible to induce attacks by glucose plus insulin, or by fluorohydrocortisone Retention of sodium, therefore, seems to be the primary factor which initiates the characteristic chain of events in an attack of periodic paralysis Conn has suggested that the high concentration of intracellular sodium is related to the characteristic hydropic vacuolization within muscle fibres which he and other investigators have observed in this syndrome The pathogenesis of the intermittent aldosteronism is not known

Electromyographic evidence suggests that conduction of the nervous impulse across the neuromuscular junction and/or along the muscle fibres is blocked (Johns Liljestrand Grob and Harvey 1955) A disturbance of membrane permeability may thus be responsible for the phenomena of transfer of potassium ions and the disorder of conduction

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PORPHYRIA

Porphyrins are pigments which exist in Nature in both free and combined forms The porphyrin structure is present in haemoglobin and in certain respiratory enzymes and consists essentially of four pyrrole units linked in a ring by methene (—CH =) bridges The por

phyrins themselves contain no iron Haematin (or haem) is an iron derivative of porphyrin (i e a metallo porphyrin) which unites with globin (a protein) to form haemoglobin (Chandler Harrison and Rimington 1939 Watson 1951) (For further details see Chapter 12)

Porphyria is an inborn error of porphyrin metabolism characterized by the overproduction of certain porphyrin substances There is defective porphyrin synthesis Artificial porphyrins play no part in human disease When porphyrins are found in the urine they occur as uro porphyrins coproporphyrins or as a colourless chromogen—porphobilinogen They are also excreted in the faeces Porphyrinuria does not necessarily mean porphyria as porphyrins may appear in excess in the urine in liver disease in anaemia or after intoxication by certain chemicals in otherwise healthy persons Porphyrin as such is probably never excreted primarily through the kidney but is formed in the urine through the condensation of two molecules of porphobilinogen This condensation largely depends upon external factors such as temperature and reaction of the urine Porphyrin has never been demonstrated in the blood of acute porphyrics but several times in congenital porphyria It is sometimes difficult to say whether the disturbance of porphyrin metabolism in a given case is constitutional or of infectious or toxic origin The symptomatology of the acute episode in familial porphyria and in acute toxic porphyria is identical In patients with familial porphyria acute episodes may also be precipitated or aggravated by certain chemical substances In a study of a large affected family group (Dean and Barnes 1955) acute porphyria the chronic cutaneous form and symptomless porphyrinuria were all encountered There was a characteristic Mendelian dominant inheritance without sex linkage

In view of the fundamental nature of the metabolic disorder it is not surprising that the clinical manifestations of porphyria are protean These may be cutaneous visceral or mixed in character The classification of the porphyrias has undergone significant changes in recent years It is now considered that so far as uroporphyrin excretion is concerned the metabolic error is quantitative rather than qualitative and that the disease can be divided into two principal categories (Aldrich Lobbe and Talman 1955) These are (1) *Erythropoietic Porphyria* which results from abnormal porphyrin or haemoglobin formation in the bone marrow and (2) *Hepatic Porphyrias* which show normal bone marrow findings but high concentrations of porphyrins and porphyrin precursors in the liver The first is essentially a congenital condition which manifests itself at any age by vesication pigmentation or the development of hirsuties Photosensitivity dates from birth in these cases and deposition of porphyrin in the bones and teeth takes place In the second group there is the classical acute intermittent type and

the chronic cutaneous type (cutanea tarda) It is in acute intermittent porphyria in which the derangement of porphyrin metabolism probably lies in the liver that dramatic nervous disorders may arise

An episode of acute porphyria may arise spontaneously or be precipitated or aggravated by barbiturates aliphatic sedatives sulphonamides or thiopentone anaesthesia Serious symptoms may follow abdominal operations or develop during pregnancy There is usually acute severe abdominal pain with vomiting constipation and ileus During this acute phase the patient usually passes reddish brown urine which darkens on standing Pains are frequently complained of in other parts of the body and weakness of the limbs may at first escape notice The patient may be agitated or greatly distressed and require paraldehyde or morphine for relief of symptoms Hypertension and retinal artery spasm have been noted and there is usually tachycardia with transient changes in the electrocardiogram The evidence of impaired liver function can often be found

Neurological manifestations (in approximately 50% of cases) are usually ushered in by severe pains in the limbs and soon dominate the clinical picture Colic usually subsides with the onset of paralysis The patient develops weakness in proximal or peripheral parts of the limbs this may spread rapidly and result in a flaccid tetraplegia The muscles may waste and the reflexes usually disappear Retention of urine may be troublesome The muscles of the abdomen and thorax are frequently involved and death may result from the complications or respiratory or bulbar paralysis The patient s behaviour is abnormal He is usually confused irrational or deluded The pupils are often dilated This abnormal mental state may develop acutely or insidiously often before actual motor paralysis Sometimes the paralysis develops in an ascending though not necessarily symmetrical manner It is the abnormal mental state of these patients which by distracting the clinician and making formal examination of the nervous system difficult often leads to errors in diagnosis There are seldom any sensory signs and pyramidal signs are rare A curious contrast that has been noted is the presence of prominent ankle clonus with loss of the knee jerks Convulsions may occur

In a recent review of 69 cases of acute porphyria the mortality was 58% (Markovitz 1954) Thirty two patients had been mistakenly submitted to laparotomy The main clinical features were (1) abdominal pain (2) peripheral neuropathy and (3) mental or emotional disturbances

In the acute stage if the urine is reddish brown in colour the correct diagnosis should suggest itself It has been established however that in some attacks porphyrins may be absent from the urine and it is of course not uncommon for the urine to be normal in colour although

suitable tests would demonstrate the presence of porphyrins The urine may darken on standing in sunlight particularly after the addition of hydrochloric acid and it fluoresces on exposure to ultra violet light If Ehrlich s aldehyde reagent is added the urine is shaken and chloroform then added a red colour will appear in the aqueous solution Spectroscopic examination will always confirm the presence of porphyrins Porphobilinogen excretion is considerably higher in active cases of porphyria than in latent cases and is not influenced by dietary restriction of protein During remissions the usual tests for porphyrins may be negative

Recovery of muscle power is usually slow but cases have been reported in which it has been rapid and complete Even cases with bulbar palsy may recover Further episodes of paralysis may occur The potentially reversible nature of the damage to the nervous system is of great interest but despite the striking clinical findings the pathological changes in the nervous system are neither marked nor specific In fatal cases patchy demyelination and destruction of axis cylinders have been observed in peripheral nerves The general appearance and pattern of these lesions have been likened to those of ischaemic neuropathy In the central white matter also focal demyelination occurs and there may be some reaction in nerve cells It has been suggested that these changes are manifestations of widespread ischaemia and not the primary features of the disorder In a study of 5 fatal cases of acute porphyrin Hierons (1957) considered that the changes in the peripheral nerves and the anterio hour cells were a result of the metabolic disorder and not due to vascular spasm Extensive vascular lesions can occur in the brain but appear to be secondary to hypertension and respiratory paralysis Although no vasoconstrictor substance has been found in patients with acute porphyria hypertension is not uncommon and there are recent reports which claim alleviation of severe episodes by the use of various vasodilator drugs Kezdi (1954) reported loss of the carotid sinus reflex during episodes of hypertension and tachycardia in acute porphyria

The porphyrin content of brain and spinal cord in fatal cases is not increased so the neurological disorder cannot be directly ascribed to the porphyrin compounds themselves There are no neurological changes in congenital porphyria The relationship between the derangement of porphyrin metabolism and the production of morphological changes and nervous symptoms remains obscure

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HEPATOLENTICULAR DEGENERATION

(Wilson's Disease)

Hepatolenticular degeneration is a familial disease in which cirrhosis of the liver is associated with degenerative changes in the brain mainly affecting the lenticular nuclei There are two metabolic abnormalities present in this disease which appear to place it in that group of dis orders termed inborn errors of metabolism These errors are con cerned with the metabolism of copper and of amino acids The precise relationship between these disturbances is not known

The classical features of the disease described by Wilson (1912) are those of extrapyramidal motor disorder It is known however that disease of the liver is invariably present before nervous manifestations occur Symptoms of portal hypertension jaundice splenomegaly with anaemia and haemorrhagic phenomena may be the sole clinical mani festations of the disease during this phase They usually subside and with the development of neurological disabilities symptoms of hepatic disorder are usually in abeyance and tests of hepatic function often

reveal little abnormality Hepatolenticular degeneration is rarely diagnosed therefore before the neurological symptoms make their appearance This sequence of clinical events constitutes one of the distinctive features of the disease and it is probable that in the literature of splenic anaemias these facts have not been sufficiently appreciated Warnock (1952) in an analysis of almost all the existing case reports showed that approximately 60% of cases never exhibit outward evidence of liver disease after the onset of nervous symptoms whereas in the pre neurological phase one third of all the cases had severe hepatic symptoms Jaundice ascites anaemia gastro intestinal symptoms and enlargement of liver and spleen were the commonest of these manifestations Franklin and Bauman (1953) found clinical signs of liver disease in seven out of eleven cases of Wilson s disease five of these developed symptoms of liver disease before any nervous symptoms made their appearance It is no longer true to say therefore that the hepatic disorder of Wilson s disease cannot be diagnosed clinically Hypogonadism and cutaneous pigmentation are two other observations which have been periodically made in this disease

The disease is strongly familial but there is no clear case of direct inheritance although it is possible that it is inherited in an autosomal recessive manner (Bearn 1953) In a clinical biochemical and genealogical study of sixty members of one affected family Heuyer Baudouin Azima Faure Jerome and Schmitt (1953) recorded two deaths from the characteristic form of the disease one from jaundice one from ascites and two in infancy from unknown cause Copper and amino acid studies were made in five members of the second generation in sixteen members of the third generation (the patients) and in four members of the fourth generation Only two had hypercupraemia three had hypocupraemia No disturbance of amino acids was found None of these subjects had Wilson s disease This study showed therefore that the blood relatives of patients with Wilson s disease had either the full syndrome or none of its constituent parts

From a neurological aspect there are two types of the disease Wilson described the chief features as generalized tremor dysarthria dysphagia muscular rigidity and hypertonicity emaciation spasmodic contractions contractures and emotionalism Pyramidal function remains intact and there are no sensory disturbances The onset of nervous symptoms which is usually insidious is in childhood or adolescence but deterioration may be quite rapid with a fatal outcome in a few months or at most several years A common early sign consists of a deterioration of writing A coarse action tremor develops in the limbs and is associated with plastic muscular rigidity the adoption of bizarre attitudes a spastic smile and difficulty in swallowing and speaking The fixed vacuous smile disturbed speech and salivation may

suggest mental deterioration The child is usually emotional and liable to bouts of crying and laughter In the terminal stages of the disease there may be widespread muscular tetanic spasms with opisthotonos and drenching sweats

In a second clinical type the onset is much later in adult life and the whole process is more protracted The outstanding symptom is tremor there is little muscular hypertonicity and difficulties in speaking and swallowing are not experienced for some years The face takes on an immobile Parkinsonian expression and some degree of emotional instability is often present *It is this type of the disease which has been* referred to as pseudo sclerosis because of the apparent similarity it bore to cases of disseminated sclerosis This clinical classification is not absolute and there are various intermediate forms In some cases torsion dystonia is the prominent feature but common to most types of the disease and present in some 80% of reported cases is the so called Kayser Fleischer ring This consists of corneal pigmentation which cannot always be detected by ordinary methods of examination, and may require slit lamp investigation It is found in no other disease That it is to some extent due to deposition of copper is suggested by the observation that it diminishes in some cases treated by dimercaprol (Denny Brown and Porter 1951) The pigmentation did not diminish in the case treated for four years by Warnock and Neill (1954)

Greenfield (1953) has pointed out that there are also sporadic non familial cases resembling Wilson s disease in their motor and psychical symptoms and showing evidence of liver disorder, in which the typical biochemical changes and Kayser Fleischer ring are absent Histologic ally but not chemically his case appeared to be one of hepatolenticular degeneration so that the classification of these cases will require further study

Amino acid Excretion

In 1948 it was first reported that there was in this disease an increased urinary excretion of amino acids and that this took place in the absence of hepatic failure (Uzman and Denny Brown) Further investigations confirmed these findings and demonstrated that this increased amino acid excretion is due to a renal defect *and is not associated* with any excess of amino acids in the blood (Porter 1949 Cooper, Eckhardy Faloon and Davidson 1950 Dent and Harris 1951) Amino aciduria is not a feature of any other disorder affecting the basal ganglia (Porter 1949, Spillane, Keyser and Parker 1952) and in hepatolenticular degeneration is not confined to cases with severe liver disorder It is almost always present and is universal in type i e all ten essential amino acids are involved and also the non essential amino *acids* glycine and alanine (Matthews Milne and Bell 1952) Unlike normal

individuals those with Wilson s disease have changes in the amino acids in the urine depending on the amount of protein in the diet (Stein Bearn and Stanford Moore 1954) The amino aciduria has also been demonstrated in otherwise healthy siblings and there is a high incidence of cirrhosis in relatives (Uzman and Hood 1952) These authors also noted an increased urinary excretion of dicarboxylic amino acid peptides in relatives Dent and Harris (1951) claim that amino aciduria is absent in cases without corneal pigmentation They suggest that cases of abnormal excretion of amino acids secondary to a renal defect fall into two main classes—the cystine lysine type or classical cystinuria in which there is a specific defect in relation to these substances and secondly the type showing a generalized amino aciduria The second class may be further subdivided into cases of (1) the Fanconi syndrome (2) Hepatolenticular degeneration The skeletal abnormality in the one syndrome and the brain lesions in the other clearly separate the two conditions All three varieties of renal amino aciduria appear to be hereditary abnormalities The evidence suggests that the finding of amino aciduria in apparently healthy younger siblings of patients with hepatolenticular degeneration means that they will develop clinical evidence of the disease at a later date In contrast similar urinary abnormality in siblings of patients with the Fanconi syndrome or classical cystinuria is not necessarily followed by any disability although cirrhosis may eventually occur (Matthews *et al* 1952)

Gilsanz Segovia and Castro Mendoza (1955) found no evidence that renal function was impaired in Wilson s disease as in the Fanconi syndrome The increased ammonio poiesis seemed to depend upon the increased amino aciduria In H disease (Baron Dent Harris Hart and Jepson 1956) the renal amino aciduria has a different pattern and there is photosensitivity and periodic cerebellar ataxy

Abnormalities of Copper Metabolism

Intoxication with or abnormal metabolism of heavy metals in this disease was suspected because of the pigmentation of the cornea the skin and other organs Accumulation of copper in the liver and later in the brain was reported many years ago and has been adequately confirmed (Haurowitz 1930 Luthy 1931 Glazebrook 1945 Cummings 1948) In recent years intensive studies of copper metabolism in this disease have shown that there is (1) *increased urinary excretion of copper* (Mandelbrote Stanier Thompson and Thruston 1948) (2) *reduced faecal excretion of copper* resulting in a strongly positive copper balance (Zimdahl Hyman and Cook 1953) (3) *deficient serum copper* in the form of the blue metalloprotein complex caeruloplasmin isolated in 1947 by Holmberg and Laurell (Scheinberg and Gitlin 1952) (4) *low serum copper-oxidase activity* (Bearn and Kunkel

1952) and that (5) *patients with the disease retain a greater amount of dietary copper* than do normal subjects (Zimdahl *et al* 1953 Cartwright Hodges Gubler Mahoney Daum Wintroble and Bean 1954 Matthews 1954) (6) *the urinary excretion of copper is increased* and the neurological symptoms are to some extent relieved by *the administration of dimercaprol* (BAL) (Mandelbrote *et al*, 1948 Porter 1949 Cumings 1951 and 1954, Denny Brown and Porter 1951 Matthews *et al* 1952 Warnock and Neill 1954 and others) treatment with dimercaprol does not influence the amino aciduria In the case reported by Streifler and Feldman (1953) treatment with BAL eliminated also the electro encephalographic abnormality (7) absorption and excretion studies of radioactive copper suggest that in Wilson s disease there is *overabsorption of copper from the gastro intestinal tract* the newly absorbed copper is attached to the albumin fraction of the plasma proteins and in patients with Wilson s disease the normally rapid transference to caeruloplasmin does not occur (Earl Moulton and Selverstone 1954 Matthews 1954 Bearn and Kunkel 1954) Radioactive copper given by mouth to healthy people at first attaches itself to the albumin fraction of the serum protein but within twenty four hours transfers *itself to the globulin fraction In Wilson s disease this transfer* is delayed or does not take place the copper remains with the albumin fraction There is therefore a defective synthesis of caeruloplasmin

The Pathogenesis of the Disorder

Uzman Iber Chalmers and Knowlton (1956) summarize the two *principal theories of the pathogenesis of Wilson s disease* (1) It is a congenital familial defect due to overabsorption of copper from the gastro intestinal tract leading to cirrhosis renal tubular damage and central nervous system poisoning Deposition of copper in the liver and brain occurs because of the different physico chemical state of plasma copper in this disease there is an inability to synthesize caerulo *plasmin (2) It is a genetically determined defect of* protein metabolism which leads to the formation of protein or polypeptide residues with high affinity of copper binding Urinary excretion of copper peptides produces amino aciduria by competition for tubular absorption According to this theory the accumulation of copper in the tissues is a secondary phenomenon arising from the primary defect in protein *metabolism In support of this theory* Uzman *et al* report that liver biopsy studies in a patient with hepatolenticular degeneration showed that the liver contained a protein fraction possessing high copper binding properties The excessive deposition of copper may be related to this rather than to the presence of abnormal serum copper (Chalmers Iber and Uzman 1957)

The clinical manifestations of the disease appear to result from the

deposition of copper in the basal ganglia What remains obscure is the reason why the brain and especially the basal ganglia are chosen for this excessive deposition of copper There is evidence that the form in which it is laid down in the brain in Wilson s disease differs from the normal (Porter and Folch 1957)

The sequence of these biochemical lesions needs to be established because it is becoming clear that treatment with dimercaprol is most likely to yield results if it is begun early in the course of the disease and maintained over long periods The injections are painful and often associated with side reactions Walshe (1956) suggests that penicillamine (B B dimethyl cysteine) which he has found eliminates copper from the human body in controls and in patients with Wilson s disease may prove useful in treatment Ravin (1956) describes a simple colorimetric technique for the estimation of the enzymatic activity of serum copper oxidase decrease of which may be one of the earliest signs of the disease Bickel Neale and Hall (1957) in an extensive trial of copper removing agents (BAL molybdenum and versene) obtained disappointing clinical results They were not able to produce a negative copper balance for long periods and suggest that treatment by the administration of caeruloplasmin will require investigation

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THE NEUROLOGICAL COMPLICATIONS OF LIVER DISEASE

The development of modern knowledge of the relationship between disordered liver function and disturbances of the nervous system may be considered to have started with the studies of Frerichs (1860) Recent interest in this subject has served to recall his classical description of the symptoms and signs of cerebral disorder in a series of 31 patients with acute liver atrophy in which he also recorded his discovery of leucine and tyrosine crystals in the urine of these patients Since Frerichs s day most accounts of the clinical features of the nervous disturbances brought about by disease of the liver have stressed the varying acuteness or insidiousness of the onset the reversibility of the symptoms and the alterations of consciousness behaviour and reflex activity Cirrhosis hepatitis and liver necrosis have provided the majority of cases but in recent years the neurological syndrome has also been observed following porta caval anastomosis and the use of new drugs

The cerebrospinal fluid of these patients was found to be normal on routine testing and until thirty years ago post mortem examination of the brain had disclosed little information It was already appreciated however that in the chronic form of hepatolenticular degeneration (Wilson s disease) there was a peculiar enlargement of the protoplasmic astrocytes of the cortex and basal grey matter These same glial changes were ultimately found in cases of hepatic coma of varying aetiology and Adams (1949) and Adams and Foley (1953) in an extensive neuropathological study of 165 cases of fatal liver disease concluded that the essential feature consisted of a diffuse hyperplasia of protoplasmic astrocytes in the lenticular and dentate nuclei cerebral cortex diencephalic and other brain stem nuclei with only relatively minor alterations of parenchymal structures This type of change was found in all types of liver disease but tended to be more pronounced in the chronic progressive forms such as haemochromatosis Laennec s cirrhosis and subacute and chronic forms of hepatitis and in those cases with prolonged coma It is not claimed that the neurological symptoms are the result of this astrocytosis but that the latter is highly characteristic of liver disease seems not to be in doubt

The Clinical Syndrome

Disorder of consciousness is the outstanding feature but its manner of development and the disturbances which may accompany it depend

to some extent on the type of case In cirrhosis which is by far the commonest type of liver disease seen in a general hospital terminal coma is usually preceded by a stage in which the level of consciousness fluctuates sometimes remarkably and over long periods of time The earliest sign probably consists in reduced awareness or alertness the patient is lethargic and speaks little He may drop off to sleep unduly and there may be periods of confusion in which speech is slurred and orientation impaired He may become restless and wander aimlessly or void urine inappropriately or incontinently These symptoms lose none of their significance if by chance they are transient, relapse and further dangerous signs are the rule and sooner or later consciousness is progressively lost

When the primary liver disorder is one of acute necrosis such as occurs rarely in viral hepatitis or in some forms of chemical poison ing the mode of onset of the nervous disturbance is naturally more acute In hepatitis this may be ushered in by a deterioration in the general condition of the patient or by persistent nausea and vomiting A phase of restlessness and excitability may precede the stupor and coma Attacks of screaming delirium or frank mania are not un common and make nursing difficult Convulsions may occur There may be dehydration and foetor hepaticus

A third group comprises those patients with chronic liver disease who remain reasonably well and ambulant until something disturbs the precarious balance of liver function the state of the portal systemic collateral circulation or the level of toxic nitrogenous substances in the blood stream It may be a bout of acute alcoholism or an attack of pneumonia or other infection which precipitates trouble In other cases an acute gastro intestinal haemorrhage is responsible Lastly it may be some therapeutic measure such as the administration of morphia paraldehyde or barbiturate or the administration of a high protein diet or methionine or ammonium chloride which endangers life Surgical procedures including abdominal paracentesis for the relief of ascites have also been held responsible Patients with large portal systemic collateral veins which have developed spontaneously or following surgical porta caval anastomosis are particularly susceptible to the toxic action of a high protein diet or the presence of blood in the gastro intestinal tract

In these groups of cases clinical examination during the phase of transient or persistent disturbance of consciousness will reveal signs of motor disturbance The most characteristic is the flapping tremor of the outstretched hands Denny Brown (1946) described as the most striking and most constant single symptom in Wilson s disease the wing beating (*flugelschlagen*) tremor of Strumpell It is periodic ir regular in amplitude and consists of a rhythmical flexion-extension

movement at the wrist joints when the arms are outstretched There may also be lateral movements of the separated fingers and flexion extension movements at the metacarpo phalangeal joints The tremors subside in complete repose and are increased by voluntary movement and thus differ from the common tremors of other diseases of the extrapyramidal system Adams and Foley (1949 and 1953) found a coarse flapping tremor of the outstretched hands to be one of the most useful signs of impending cerebral disorder in patients with all forms of liver disease It was present in 17 of the 18 patients described by Sher lock and her colleagues (1954) Most authors have also commented on the presence of muscular twitching fluctuating muscular rigidity grimacing and pouting sucking and grasp reflexes and of characteristic pyramidal signs Frank Parkinsonian signs are uncommon but Walshe (1951) has seen cog wheel rigidity and choreiform movements

Against this background of widespread disturbance of the nervous system the clinician may find the classical signs of chronic liver disease or evidence of acute hepatitis or liver necrosis Malnutrition and/or signs of alcoholic neuropathy (polyneuritis Wernicke s encephalo pathy Korsakoff s syndrome) may also be present

When the neurological syndrome progresses and coma intervenes the limbs become flaccid restlessness and clonus subside but the flapping tremor may persist for some time and may still be initiated by placing the patient s arms in the outstretched position There is con siderable variation in the way in which the patient may sink into stupor or coma The deterioration may be rapid or slow progressive or halting and restoration of consciousness when it takes place may similarly vary in its speed and completeness The comatose state itself may last from several hours to a week or ten days but recovery from deep coma is uncommon and nearly always transient

The electro-encephalographic disturbances were first described by Foley Watson and Adams (1950) and consist of paroxysms of bilaterally synchronous symmetrical high voltage slow waves in the delta region of 1 5 to 3 per second interspersed with or superimposed on relatively normal alpha waves They appear earliest in the frontal and central regions and tend to spread posteriorly They are not constant or specific and they tend to disappear in the stage of deep coma

The term portal systemic encephalopathy was introduced to describe these chronic or intermittent neurological syndromes which so often terminate in hepatic coma (Sherlock *et al* 1954) The latter represents the grossest manifestation of the disordered brain liver relationship It is postulated that whether the encephalopathy is acute or chronic it results from such factors as impaired liver function shunting of portal blood to the systemic circulation and the presence of nitrogenous material in the intestines Whether some specific disturbance exists in

such circumstances or whether a chain of events is initiated in a variety of ways is not clear The similarity between the acute encephalopathy of hepatitis or liver necrosis and the spontaneous or induced episodic cerebral disturbance in chronic liver disease suggests that some specific biochemical lesion is common to both states When such a neurological syndrome confronts the clinician it is not difficult to appreciate that disease of the brain and not of the liver comes first to mind In the acute case when there is no history of chemical poisoning recent inoculation or contact with a case of hepatitis, and when jaundice has not appeared correct diagnosis may be delayed In the intermittent type of case a metabolic disorder is more likely to come to mind and signs of cirrhosis sought When there is progressive deterioration of personality and intellect with little or no fluctuation an admittedly rare type disease of the liver may never be suspected during life As in certain other diseases such as acute porphyria islet cell adenoma of the pancreas or phaeochromocytoma what first prompts the clinician is the index of suspicion he has acquired for those particular diagnostic problems Liver function tests will usually be abnormal in cirrhosis but other biochemical tests are not very helpful apart from revealing high blood ammonia levels Summerskill Davidson Sherlock and Steiner (1956) have found that assessment of nitrogen tolerance is the most specific investigation Deterioration usually follows the administration of ammonium chloride or methionine in doses of 10 g daily or if the dietary protein exceeds 60 g daily Improvement is obtained by re stricting dietary protein to 20 g daily

The Biochemical Lesion

The cause or causes of the hepatic comas and allied neurological disturbances are not known Presumably there is a failure of the de toxicating function of the liver or liberation of a toxic by product of its disordered metabolism As a result brain function may be disturbed by different biochemical lesions from time to time The recognition of the several predisposing factors already mentioned and the common finding of a raised level of blood ammonia suggest that a disorder of nitrogen metabolism is one important factor The normal blood ammonia level is approximately 50 μg /100 ml and in hepatic coma it commonly rises to 150 to 250 μg /100 ml There are difficulties in the techniques of estimation of blood ammonia and it seems not unlikely that the levels obtained in peripheral venous blood do not truly reflect the concen tration of ammonia reaching the brain The methods used have usually depended on the micro distillation of ammonia from the blood sample and it has been pointed out that these methods measure not blood ammonia but some unstable compound which is broken down to liberate diffusible alkali (Walshe 1956) Ammonia is formed where

amino acids are deaminized this takes place in the liver and in the intestines as a result of bacterial action It is a highly toxic substance and is normally combined with alpha ketoglutaric acid to form glutamic acid with glutamic acid to form glutamine or made into urea A high CSF glutamine level has been found in hepatic coma (Walshe 1955) The nature of the toxic action of the nitrogenous substance is not understood but it is possible that a failure of ammonia binding mechanisms of the brain is involved The administration of sodium glutamate in hepatic coma was introduced in the hope that it would combine with ammonia to form glutamine The toxicity of methionine in patients with severe liver disease is now well established but its action does not seem to depend on ammonia production in the intestine (Phear Ruebner Sherlock and Summerskill 1956) Methionine sulphoxide a glutamic acid antimetabolite has been found in the plasma and cerebrospinal fluid of patients with hepatic coma and it has been suggested that it might interfere with ammonia binding mechanisms in the brain (Walshe 1953) The isolation from the urine of a patient with foetor hepaticus of methyl mercapton and dimethyl sulphide is reported by Challenger and Walshe (1955) These substances are derivatives of methionine which accumulates in the blood stream in hepatic coma and their detection directs attention to toxic metabolites other than ammonia in these hepatic comas

The reader is referred to the appended references for further information concerning the pathogenesis of hepatic coma (See also Chapter 5)

Principles of Treatment

As in the treatment of all comatose patients there are general principles to guide the clinician such as (1) the provision of an adequate supply of calories (2) the maintenance of fluid and electrolyte balance (3) adequate oxygenation (4) the prevention of infection

The caloric requirements of a patient in coma are not clearly known One to two thousand calories daily is a reasonable estimate fever and restlessness may necessitate a higher intake Methods of feeding will be influenced by fluctuations of consciousness frequent small feeds by mouth tube feeding and intravenous 25% glucose may all be necessary at different stages of the illness Regulation of fluids and electrolytes can be accomplished only by measurement of the total intake and out put The balance sheet which also includes estimate for fluid provided from the metabolism of food and for insensible loss is of greatest value Electrolyte disturbances are common and clinical improvement may follow their correction Oliguria may be due to dehydration or directly to the liver disease The prevention of pneumonia by expert nursing and the use of antibiotics and of urinary infection from catheterization

are obvious aims There is no specific form of therapy for hepatic coma but the use of glucose and the restriction of protein intake follow naturally from the ideas outlined concerning aetiology Antibiotics including aureomycin and tetracycline and the use of purgatives and enemata help to reduce the production of toxic nitrogenous substances in the intestines There are variable reports concerning the value of glutamic acid a fall in the blood ammonia is not uncommon but there is little improvement to be seen in the acute cases The toxicity of many hypnotics and sedatives in the presence of liver disease constitutes a considerable problem Many of these patients may have phases of restlessness and noisy delirium and it becomes difficult to estimate the danger entailed in using sedatives The longer acting barbiturates which are largely excreted by the kidneys may be used cautiously morphia and its derivatives and paraldehyde are contra indicated

See also the discussion in Chapter 5

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INDEX

Acetylcholine
in convulsions 293
in myasthenia 321
in nerve impulse 294
Achlorhydria
in anaemia of pregnancy 270
in hypopituitarism 282
in iron absorption 216
in myxoedema 279
in sprue 267
Acid base
balance 172–178
composition of body fluids 19
Acidosis, 34–36
in anoxia 180
with diuretics 27 28
with exchange resins 7
in Fanconi syndrome 64
hyperchloraemic 65
hypochloraemic 28
metabolic 34 173
in osteitis fibrosa cystica 205
in renal failure 67
respiratory 34 172
in uraemia 59
in urine acidity 48
Acromegaly heart disease in 148
ACTH
on haematopoiesis 287
in injury 97
in myelomatosis 253
Addisonian anaemia 266
aetiology of 260
therapy 266
Addison's disease hypoglycaemia in 304
Adipose tissue
estimation of 5
in nutrition 4
total 5
Adrenal gland
in ascites 125
in bone injury 83
in haematopoiesis 284
in injury 81 88 96–97
in oedema, 76
pre-operative activity 76
and sodium excretion, 158
and sodium re-absorption, 47
in thyrotoxicosis 90
Adrenalectomy 94
Adrenalin
in hypoglycaemia 290 30
in injury 96 98
in periodic paralysis 3 6
in thyrotoxic heart disease 146
Adrenalin test in Von Gierke's disease 135
Albumin
in flocculation tests 129
in jaundice 119
in liver disease 127
in myelomatosis 253
in nephrotic syndrome 56
therapy of ascites 140
Albuminuria (*see* proteinuria)
Alcohol
in cirrhosis of the liver 119
in fatty liver 113
Aldosterone 41
in congestive heart failure 158 160
in injury 94
in oedema 26
in periodic paralysis 327
Alimentary secretions, 21
Alkali reserve (*see also* bicarbonate) 175
Alkalosis 36
with diuretics 7
in low salt syndrome 8
metabolic 36 173
in potassium depletion 30
respiratory 36 173
urine acidity in 48
Alveolar air
in lung function 172
in oxygen therapy 186
Amaurotic family idiocy 314
Amino acids,
in heart metabolism 153
in myelomatosis 251
Aminoaciduria,
in jaundice 134
in liver disease 129
in Wilson's disease 334
Aminopterin 64
Ammonia
blood level 342
in Fanconi syndrome 65
in liver coma 123 142, 342
renal tubular acidosis 66
in uraemia 59
in urine acidity 48

Ammonium chloride
in acidosis 35
in ascites 141
with diuretics 27
in liver coma 342
with mercurial diuretics 163
Amyloidosis 151
Anaemia (*see also* megaloblastic anaemia)
achrestic 273
Addisonian 266
in Addison s disease 280
in hypogonadism 281
in hypopituitarism 281
of infection 222
of liver disease 246
with malabsorption 267
megaloblastic (*see also* megaloblastic anaemia) 258–275
in myxoedema 278
in renal disease 248
with thymoma 280
Anaesthesia
cerebral metabolism in 293
in injury 89
Aneurin (*see* Vitamin B_1)
Anoxia 180
in lung function 172
Antibiotics in liver coma 124 344
Anti-diuretic hormone
in ascites 125
in congestive heart failure 158 161
in oedema 26
in water re absorption 45
Anuria
in acute renal failure 61
in uraemia 57
Aortic body receptors, 173
Apoferritin 217
Appetite centres 3
regulation 2
Argentaffinoma 149
Arginine
in cystinuria 65
therapy of liver coma 142
Arsenic in neuronal metabolism 298
Arteriosclerosis (*see also* atherosclerosis) 166–171
Ascites, 124
Ascorbic acid (*see* Vitamin C)
Aspirin in methaemoglobinaemia 243
AT 10 in hypoparathyroidism 210
Atherosclerosis 166–171
in myxoedema 148
Auricular fibrillation 146

BAL *(British Anti Lewisite) 65 337*
Band keratopathy 208 334
Barbiturates
in liver coma 344
Barbiturates and megaloblastic anaemia 273
and porphyria 330
Basal metabolic rate *2 11*
Bence Jones protein 251
Beriberi (*see also* Vitamin B_1) 152 297
Bicarbonate 174 175
in acidosis 34 35
with carbonic anhydrase inhibitors 164
in extracellular fluid 19
in intracellular fluid 19
in iron absorption 217
in low salt syndrome 28
with mercurial diuretics 163
in potassium depletion 30
in renal failure 62
in renal tubular acidosis 66
in uraemia 59
in urine acidity 47
***Bicarbonate re-absorption** 164*
Bilirubin
detection in urine 130
in jaundice 317
in kernicterus 317
in liver disease 130
in pruritus 322
Biliverdin 120
Biluria 120
Blood brain barrier 288
Blood pressure
in acute nephritis 51
in aldosteronism 42
in amyloidosis 151
in anoxia 180
in atherosclerosis 166
in beriberi 152
in injury 89 98
in obesity 7
in porphyria 330
in under nutrition 12
in uraemia 56 59
Blood volume
in liver disease 246
in myxoedema 279
in nephritis 51
in polycythaemia 224
in renal disease 248
Body weight 1 3
in bone injury 83
following injury 77 79 81
ideal 5
Bone
in hypoparathyroidism 209
in osteitis fibrosa cystica 206
in osteomalacia 203
in osteoporosis 200
in porphyria 329
Bone marrow 213
in iron deficiency 219

Bone marrow—(*continued*)
in liver disease 247
in macroglobulinaemia 256
in myxoedema 279
in porphyria 329
in renal disease 249
in sprue 267
Botulinism 322
Brain
in amaurotic family idiocy 315
carbohydrate store 290
chemical constitution of 289
in convulsions 292
in Gaucher's disease 314
in hypoglycaemia 305
in kernicterus 316
in liver coma 339
in Niemann Pick's disease 314
oxygen consumption of 289
in starvation, 291
Bromsulphthalein excretion 131 134

Calcium
in acidosis 35
in bone disease 198
in extracellular fluid 19
in hyperparathyroidism 205 208
in hypoparathyroidism 208 210
and iron absorption 216
in myelomatosis 250
in osteitis fibrosa cystica 205
in osteomalacia 203 204
in osteoporosis 200
in pseudo-hypoparathyroidism 210
in renal failure 62
in renal tubular acidosis 65 66
in sprue 268
in uraemia 59
Calcium excretion
in hypoparathyroidism, 209
in osteitis fibrosa cystica 206
in osteomalacia 204
in osteoporosis 200
Calorie balance 1
Calorie intake
appetite regulation 4
in beriberi 152
in liver disease 138
Carbohydrate
in brain 289 290
in cerebral metabolism 290
in glycogen storage disease 150
in liver disease 138
in nerve impulse 94
Carbon dioxide
in cerebral circulation, 287
and lung function 173
measurement 193
in oxygen tents 189 190

Carbon dioxide
in respiratory control 172
in urine acidity 48
Carbonic anhydrase inhibitors 164
in congestive heart failure 164
in oedema 27
in potassium secretion 47
Carcinoid tumour 149
Cardiac failure 156–164
in acute renal failure 63
in extrarenal uraemia 68
in nephritis 51
Cardiac output
in beriberi 152
in myxoedema 147
in oedema 26
in thyrotoxic heart disease 146
Cardiomegaly 148
Carotid body receptors 173
Casein
in fatty liver 112
in hepatic necrosis 114 118
Catechol amines, 96
Central nervous system in anoxia 180
Cerebral
blood flow 288
in convulsions 29
circulation 287
metabolic rate 289
metabolism 89–94
in anaesthesia 293
in convulsions 29
Cerebromacular degeneration, 314
Cerebrosides, 311
Chastek paralysis 296
Chloride
in acidosis 34
in extracellular fluid 19
in injury 100
in intracellular fluid 19
with mercurial diuretics 163
in sodium re-absorption 47
Cholesterol 167
Choline
in alcoholic cirrhosis 119
in atherosclerosis 170
in fatty liver 112 142
in liver tumours 119
in myasthenia, 321
in peripheral neuritis 299
Chromatography
in jaundice 134
in liver disease 129 135
Citrovorum factor (*see also* folinic acid), 64
Cobaltous chloride in anaemia
of hypopituitarism, 282
of renal disease 49
Coeruloplasmin, 329
in Wilson's disease 335

Congestive heart failure 156–164
Convulsions
in acute nephritis 52
cerebral metabolism in 292
Copper
in cerebral metabolism 296
in hepatic necrosis 117
metabolism 228
in Wilson s disease 65 335
Coproporphyrin,
in erythrocyte 233
in lead poisoning 234
Corticoids
in aldosteronism 42
in injury 79 80 83
in liver disease 126
plasma level 92
Corticotrophin (*see* ACTH)
Cortisone 93
in cerebral metabolism 290
on haematopoesis 282
in liver disease 143
in macroglobulinaemia 256
in nephrotic syndrome 55
in osteoporosis 199
in water re absorption 45
***Creatine* phosphate**
in brain 293
in convulsions 293
Creatinine in renal function 49
Cryoglobulinaemia 254
with macroglobulinaemia 256
Curare 322
Cystine
in hepatic necrosis 114 118
and iron absorption 216
Cystinosis 64
Cystinuria 64

Dehydration (*see also* sodium depletion) 23 25
Demyelination 315
Desoxyribose 264
Diabetes mellitus 67
acidosis in 35
atherosclerosis in 167
osteoporosis in 199
Diabetic myelopathy 308
Diabetic neuropathy 307
Dialysis in acute renal failure 63
Diamox (*see* carbonic anhydrase inhibitors)
Dibothriocephalus latus, 271
Diet
in acidosis 34
in anaemia of pregnancy 270
carbohydrate in 9
in congestive heart failure 162
fat in 9
in fatty liver 113
Diet
in hepatic necrosis 113
in liver disease 138
in nephritis 52
in nephrotic syndrome 55
in obesity 7
in oedema 26
protein in 9
in renal failure 62
sodium content of 26
in under nutrition 12
Di Guglielmo s disease 272
Digitalis
in congestive heart failure 162
in heart metabolism 154
in thyrotoxic heart disease 147
Diodone
clearance 45
in uraemia 57
Diuresis
in acute renal failure 61
in urea re absorption 48
water 46 47
Diuretics
in congestive heart failure 163
in nephrotic syndrome 56
resistance to 27 163 164
in sodium excess 27

Elastin 119
Electrocardiagram
in acromegaly 148
in amyloidosis 151
in haemochromatosis 150
in potassium depletion 30
in potassium excess 31
Electroencephalogram
in hypoglycaemia 305
in liver coma 341
in pernicious anaemia 300
Electrolytes 15–40
Electromyogram
in myasthenia 320
in periodic paralysis 328
Electrophoresis 127
Emphysema
acidosis in 35
oxygen therapy in 195
Endocardial fibrosis 149
Eosinophils
in Addison s disease 280
in bone injury 83
with cortisone *283*
in Cushing s syndrome 281
in hypopituitarism 282
in injury 80 81 97
post-operative 78
pre-operative 76
Ephinephrine (*see* adrenalin)

Erlich reaction 130
Ethanolamine 112
Exchange resins (*see* resins)
Extracellular fluid 16 18
  in aldosteronism 41
  in injury 100
  in potassium depletion 29
  in potassium excess 31
  in sodium depletion 23
  in sodium re absorption 46
  in under nutrition 11
  in water depletion 32

Familial periodic paralysis 326
  in aldosteronism 42
Famine oedema 11
Fanconi syndrome 64
  osteomalacia in, 0?
  uraemia in, 56
Fat
  appetite regulation 4
  in atherosclerosis 167–170
  in injury 77 82 101
  in liver disease 138
  in under nutrition 10
Fatty acids, in heart metabolism 153
Fatty liver 111
Ferritin, 219
  in iron absorption 217
  total body 215
Fever
  in extrarenal uraemia 68
  in injury 90
Flocculation tests, 129
Fluid
  body distribution 16
  extrarenal loss 85
  total body 16
Foetor hepaticus, 1 4
Folic acid 262
  in anaemia of infancy 271
  in anaemia of pregnancy 69
  in liver disease 139 247
  in nucleic acid synthesis 65
  in sprue 68
Folinic acid 26?
Food, regulation of appetite 4

Galsbock s disease 225
Gangliosides, 311
Gastric atrophy -61
Gaucher s disease 314
Globin metabolism 314
Globulin,
  in flocculation tests 1?9
  in liver disease 1?7
  in myelomatosis, 50 251
Glomerular filtration rate 44
  in acute nephritis 5

Glomerular filtration rate
  in congestive heart failure 157 159
  in oedema 26
  and sodium re absorption 46
  and water re absorption 46
Glomerulonephritis
  acute 50
  chronic 56
Glucose
  appetite regulation, 3
  in ascites 140
  in cerebral metabolism 87 289 290
  in heart metabolism 153
  in liver coma 14
  in periodic paralysis 3?6
  renal function and 49
  and water re absorption 46
Glucose tolerance curve 306
Glutamic acid
  in brain, 292
  in cerebral metabolism 292
  in hypoglycaemia 9-
  in liver coma 123 14? 29? 343
Glycine 229
Glycogen 138
  storage disease of heart 149
Glycosuria
  in acute renal failure 61
  in Fanconi syndrome 64
  renal 66
Guanidoacetic acid 112
Gynaecomastia 1 6

Haemocentration
  in sodium depletion, 23
  in water depletion 32
Haemochromatosis, 5
  heart disease in 150
  liver cirrhosis in 117
Haemoglobin in jaundice 1 0 1 1
Haemoglobin A 236
  in sickle-cell disease -39
  in thalassaemia 236
  G 40
  H 40
  I -40
  S -39
Haemoglobin metabolism -14
  in anaemia of infection --4
  in iron-deficiency anaemia -20
Haemolysis
  in acute renal failure 60
  in anaemia of infection --3
  in liver d sease 47
  in megaloblastic anaemia -74
  in renal disease 49
  in thalassaemia -38
Haematopoiesis, control of -84
Haemopoietine 84

Haemorrhage
extrarenal uraemia in 68
in injury 89
Haemosiderin 219
in haemochromatosis 150
total body 215
Haemosiderosis, 227
following transfusion 226
Heart disease
in acromegaly 148
in amyloidosis 151
in beriberi 152
in carcinoid tumour (argentaffinoma) 149
in haemochromatosis 150
in myxoedema 147
in thyrotoxicosis 146
Heart metabolism of 153
Henderson Hesselbach equation 174
Heparin, in atherosclerosis 170
Hepatic coma 123 339–344
Hepatic necrosis 113 117
Hepatolenticular degeneration 64 117 332–337
Hippuric acid test 131
in cholecystitis 135
in liver disease 134
Hunger osteopathy 208
Hydrocortisone (*see* cortisone)
Hydrogen ion
concentration (*see* pH)
excretion 164
in urine acidity 48
5-Hydroxy Indole acetic acid 149
Hydroxycorticoids (*see* corticoids)
Hypercapnia 172
Hypercalcaemia
in osteitis fibrosa cystica 206
in osteomalacia 204
Hypercalcuria 202
Hypercholesterolaemia
in atherosclerosis 167
familial 168
in myxoedema 148
Hyperinsulinism
functional 303
organic 304
Hyperparathyroidism
in osteitis fibrosa cystica 205
in osteomalacia 203
in renal tubular acidosis 65
Hypersplenism 248
Hyperthyroidism (*see* thyroid)
Hypertonic saline
in acute nephritis 52
in congestive heart failure therapy 162
in sodium depletion 25
Hypoglycaemia 303–306
cerebral metabolism in 290
in liver disease 123 306
Hypoparathyroidism 208–210
Hypothalmus
in injury 89 98
in nutrition 3
Hypothyroidism (*see* myxoedema)

Injury 72–105
in cardiovascular disease 88
in disease 86
endocrine factors in 91–100
Inositol 170
Insulin
in cerebral metabolism 290
in periodic paralysis 376
serum levels 305
Intracellular fluid 16 19
in water depletion 32
Intracranial pressure
in anoxia 181
in hypoparathyroidism 209
Intrinsic factor 260
Inulin
clearance 44 57
extracellular fluid estimation 21
Iron absorption 215
after gastrectomy 217
in haemochromatosis 225
in iron-deficiency anaemia, 216
in pregnancy 216
site of 217
in sprue 268
binding capacity of plasma 218
in anaemia of infection 223
in haemochromatosis 225
in thalassaemia 238
deficiency in coeliac disease 269
excretion 215
metabolism 214–227
serum 218
in anaemia of infection 223
in haemochromatosis 151 218 225
in haemolytic anaemia 218
in infection 218
in jaundice 133
in liver disease 218
in pernicious anaemia 218
in pyrodoxine deficiency 218
in thalassaemia 238
stores 215
in anaemia of infection 223
in haemochromatosis 225
in iron-deficiency anaemia 219
total body 214
turnover 219
in anaemia of infection 223
in polycythaemia 224
Islet-cell tumour 304
Isoleucine 237

Jaundice 119 121
differential diagnosis of 132–134
kernicterus in 317
in liver disease 130
in Wilson s disease 332

Kayser Fleischer ring 334
Kernicterus 316
Ketosis,
acidosis in 35
in fatty liver 111
Ketosteroids (*see* corticoids)
Kidney
in amyloidosis 151
in anoxia 180
in myelomatosis 250
Kwashiorkor 113

Lactate
in acidosis 36
in beriberi 152
in cerebral metabolism 290
in heart metabolism 153
in sodium depletion 25
Lamina dura
in osteitis fibrosa cystica 206
in osteomalacia 204
in osteoporosis 200
Lathyrism 301
Lean body mass
estimation of 5
in injury 74 77 81 101
Lecithin 112
Leucine 130
Lipaemia
in fatty liver 111
in nephrotic syndrome 55
Lipidoses 311 316
Lipids, 311–316
in atherosclerosis 167
in brain 289 291
in cerebral metabolism 291
in fatty liver 113
in flocculation tests 1 9
Lipoproteins, 168 169
Liver
in anoxia 180
circulation 115
circulation in hepatic necrosis 118
circulation with posture 137
cirrhosis 111 117
coma 123 339 344
control of haematopoiesis 284
function 113
function tests 131
necrosis 113 117
tumours of 119
in Wilson s disease 117 337

Looser s zones, 203
Low salt syndrome 27
Lymphocytosis
in Addison s disease 280
in hypopituitarism 282
in thyrotoxicosis 279
Lysine in cystinuria 65

Macrocytic anaemia
in hypopituitarism 282
in liver disease 47
in methionine deficiency 115
Macroglobulinaemia 255
Magnesium 19
Marriot s diet 8
Megaloblastic anaemia, 258–275
with anti-convulsants 273
in ascorbic acid deficiency 271
in blind loop syndrome 268
in coeliac disease 269
with folic acid antagonists 273
following gastrectomy 272
in infancy 270
in liver disease 247
with luekaemia 272
in neoplasia 27
nutritional 69
in pregnancy 269
in the malabsorption syndrome 267
with tapeworm 271
Mercurial diuretics
in ascites 141
in congestive heart failure 163
in oedema 27
potassium secretion with 47
Metabolic rate 2
Methaemalbumen 246
Methaemoglobinaemia 247 45
Methionine
in fatty liver 112
in hepatic necrosis 114 118
in liver coma 118 124 140
Methopterin, 264
Methyl mercaptan 1 4
Muscle
in myasthenia 320
in periodic paralysis 3 8
Myasthenia gravis, 319
Myelomatosis, 250–54
Myocardium
in acromegaly 148
in beriberi 152
in glycogen storage disease of heart 150
in haemochromatosis 150
in myxoedema 147
Myohaemoglobin, 15
Myxoedema
anaemia in 278

Myxoedema—(*continued*)
atherosclerosis in *167*
heart disease in *147*
in hypoglycaemia *304*

Neostigmine *322* *323*
Nephritis *50–53*
Nephrocalcinosis 36 65
Nephrotic syndrome 53–56
Neuropathy
carcinomatous 301
in diabetes *307*
in porphyria *330* *331*
Nicotinamide 142
Niemann Pick s disease 314
Nitrogen balance
in bone injury 83
in burns *84*
in injury 79 81 88 90 101
in under nutrition, 11
Nor adrenaline 96
Nucleic acid 264
Nucleotide
in brain, 291
in cerebral metabolism 293
Nutrition
on cerebral metabolism 296
and liver disease 111

Obesity 7
atherosclerosis in 170
nutrition in 3
Oedema 25–26
in acute nephritis *51*
in acute renal failure *62*
in aldosteronism 42
in congestive heart failure 156–164
in famine 11
in nephrotic syndrome 54
Oestrogens
in atherosclerosis 169
in liver disease *125* *126*
in osteoporosis *199* *201*
Oliguria
in acute nephritis *51*
in acute renal failure 61
in congestive heart failure 158
in extrarenal uraemia 68
in sodium depletion 23
in uraemia *57*
in water depletion *32*
Osmotic diuresis 46 47
sodium excretion in 158
pressure *16*
Osteitis fibrosa cystica 205–208
Osteoblasts
in bone disease 198
in osteitis fibrosa cystica *206*
Osteoblasts
in osteomalacia 204
in osteoporosis 200
Osteoclastoma *206*
Osteogenesis imperfecta 200
Osteomalacia 201–204
in acidosis *35*
in Fanconi syndrome 65
in hypoparathyroidism *210*
in osteitis fibrosa cystica 207
in uraemia *60*
Osteopetrosis *198* 199–201
Oxygen consumption
of brain 289
in convulsions 293
in myxoedema 147
in thyrotoxicosis 146
in cerebral metabolism 287–290
measurement of 191
masks *184*
poisoning 194
tents 188–190
therapy 179–197
dangers 173 194
indications *182–183*
in infants *190* *196*

Palmer erythema 125
Pantothenic acid clearance 299
Para amino hippuric acid *45*
Paracentesis 141
Parathyroids
in osteitis fibrosa cystica 204
in osteomalacia *203*
in uraemia 59
Penicillamine 65 337
Periodic paralysis 326
Peripheral neuritis (*see* neuropathy)
Pernicious anaemia (*see* Addisonian)
pH
of gastric secretion in iron absorption *216*
of plasma in lung function *173*
of plasma in uraemia 59
Phenacetin
in methaemoglobinaemia 243
in sulphaemoglobinaemia *245*
Phenol red *45*
Phenylalanine 296
Phenylpyruvic oligophrenia 297
Phosphatase acid in myelomatosis *258*
Phosphatase alkaline
in bone disease 135 198
after cholecystectomy 135
in cholecystitis 135
in cirrhosis 134
in hypoparathyroidism *209*
in jaundice *132*

Phosphatase alkaline—(*continued*)
in liver disease 131
in liver metastasis 134
in myelomatosis 250
in osteitis fibrosa cystica 206
in osteomalacia 204
in osteoporosis 200
Phosphate
in acidosis 34
in acute renal failure 62
in bone disease 198
in brain 291
in convulsions 293
effect on iron absorption 216
in extracellular fluid 19
in haemochromatosis 226
in hepatic necrosis 118
in hyperparathyroidism 205 208
in injury 78
in intracellular fluid 19
in myelomatosis 250
in osteitis fibrosa cystica 205
in osteomalacia 204 207
in osteoporosis 200
in periodic paralysis 327
in pseudo-hypoparathyroidism 210
in uraemia 59
Phosphatides 311
Phosphaturia 64
Phospholipids, 167
Pigmentation
in under nutrition 11
in uraemia 58
Pituitary in aldosteronism 41
Pituitary anterior
in cerebral metabolism 290
in control of haematopoeisis 284
in injury 97
Pituitary posterior 100
(*s e also* anti-diuretic hormone)
Plasma cells
in macroglobulinaemia 255
in myelomatosis 252
Polycythaemia 244
in Cushing s syndrome 281
Polyuria
extrarenal uraemia 69
in under nutrition, 12
in uraemia 58
Porphyria 3 8 331
Porphyrin
in jaundice 171
synthesis of 229 235
Porphyrinuria 334
Portal hypertension, 1 4
Potassium
depletion 28 31
in acidosis, 35
in acute renal failure 6 63

Potassium
in aldosteronism 41 4
in anoxia 180
in body distribution 74
in congestive heart failure 158
in convulsions 293
excess 31
excretion
in injury 79
with mercurial diuretics 163
in extracellular fluid 18 29
in extrarenal loss 85
in heart metabolism 154
in injury 77 78 81 83 84 88 90 101
in intracellular fluid 19
in liver disease 140
in myasthenia 321
in periodic paralysis 327
re absorption in renal tubules 47
and renal function 47
secretion 47
with carbonic anhydrase inhibitors 164
in uraemia, 58
total body 29 73
turnover 21
in under nutrition 10
in uraemia 58
Protein
in brain 289
in liver disease 138
Proteins serum
in ascites 125
in liver disease 127
in myelomatosis 250
in nephrotic syndrome 54
in under-nutrition, 11
Proteinuria
in acute nephritis 51
in Fanconi syndrome 65
in myelomatosis, 251
in nephrotic syndrome 54–55
in uraemia 57
Prothrombin
in jaundice 133
in liver disease 122, 131
in sprue 68
Protoporphyrin in red blood cells 233
Pseudo-cholinesterase 299
Pseudo-hypoparathyroidism, 210
Pulmonary oedema
in acute nephritis 51
in acute renal failure 63
Purpura hyperglobinaemica 256
Pyridostigmine 3 4
Pyridoxine 299
Pyruvate
in beriberi 152
in carcinomatous neuropathy 301

Vitamin E 115 139 142
K 122 139
Vitamins
in liver disease 139
in liver tumours 119
Volume receptors 160

Water 15–40
in acute renal failure 62
body total 16 73
estimation of 6
brain content of 289
depletion 32
excess 33–34 89
excretion in congestive heart failure 161
mechanism of 158
intoxication 33 34 89
in sodium depletion 23
re absorption 45
in uraemia 57
Water
and renal function 45
turnover 21
in uraemia 58
Water losing nephritis 58
Wernicke s encephalopathy 297
White blood cells
in Addison s disease 280
in anaemia of pregnancy 270
effect of cortisone 283
in polycythaemia 224
Wilson s disease 64 117 332–337

Xanthine diuretics 27
Xanthomata 168

Zinc sulphate test 134
Zona glomerulosa 41

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